Ian R. Mackay
Noel R. Rose
Editors-in-Chief

Dennis K. Ledford
Richard F. Lockey
Editors

Encyclopedia of Medical Immunology

Allergic Diseases

Springer Reference

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Encyclopedia of Medical Immunology

Allergic Diseases

With 88 Figures and 107 Tables

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Introduction

The concept of an encyclopedia derives from the Greek words for gathering together or "encircling" knowledge and learning. Indeed, Diderot and the French encyclopedists of the mid 18th century aimed to bring together all of the world's knowledge in one giant publication. Our ambitions today are more modest but "encapsulating" existing knowledge of a defined topic is still a reasonable basis for decision making in the present and planning for the future. The Encyclopedia of Medical Immunology follows in the encyclopedist tradition. At the present time, however, progress is proceeding at such a rapid pace that a static volume, no matter how extensive, could never do justice to this dynamic subject. Thus our present encyclopedia is based on the concept that articles will be linked to current research and updated on a regular basis. The reader needs to gain an understanding of medical immunology not only at the date of publication, but on a continuing basis.

The immune system, as a vital component of normal physiology, participates in establishing and maintaining the well-being of the host. Its core responsibility is to prevent or control infection and malignancy. Immune functions can be divided into constituative and adaptive. Inherited innate immunity takes its origins from most primitive cellular functions of recognition and nutrition. In animals, it evolved through invertebrates as a group of formed barriers and a system of cells and cell products for promptly dealing with harmful invaders or preventing clonal amplification of malignant cells. In vertebrates, in addition to innate immunity, an adaptive immune system provides a more focused and potent response, but one that requires more time to mobilize. It utilizes a novel system of hypermutation and recombination to provide a sufficiently broad repertory of receptors to recognize and eliminate, in principle, any potential microbial invader. In establishing and maintaining such a wide repertory of recognition structures, the adaptive immune system inevitably recognizes many epitopes on molecules within the body of the host. Thus, the same protective effector mechanisms of the healthy immune system, if out of control, can produce harm in the form of the immune mediated disorders described in these Volumes.

The most frequent disorders of the immune system are deficiencies. If the immune system fails to perform its core function of protection, infectious or malignant disease can follow. Most of these immune failures result from germ line inheritance of mutations in genes regulating the innate or adaptive

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immune systems. The most frequent sign of an immune deficiency disease is infection due to one or more of the myriad microorganisms that inhabit the human environment.

A second group of immune-related illnesses results from loss of normal immunologic homeostasis. The regulatory devices that normally limit immune responses are inadequate. The failure may result from deficiencies, either inherited or acquired, of the overall regulatory machinery. Rather than a decrease in homeostatic regulation, immune disease can result from augmented immune responses. Powerful adjuvants, providing the non-antigen-specific signals, may overcome even normally functioning immune regulation.

Both types of immune-mediated disease are considered in our encapsulated knowledge. Allergies result from exposures to foreign substances that are harmless in the majority of individuals. As a group, allergic diseases affect at least 10% of the population and appear to be increasing over time in many populations. In contrast to an exaggerated response to foreign antigens, autoimmunity is the consequence of the "forbidden" recognition of some antigens in the host's body. Like allergic disease, autoimmune disease represents an uncontrolled immune response. Because allergic and autoimmune diseases can occur in different organ systems in the body, they can differ greatly in their clinical presentation, even though they share many genetic and regulatory features.

The goal in all medical immunology is to alleviate or prevent illness. If a disease is related to an inadequate immune response or to an overwhelming challenge, an intervention in the form of vaccination is a historically proven approach. Preventive vaccinations may be the most successful public health measure of the 20th century. New vaccines directed to oncoming newly emerging infectants or subtypes remains a major goal of current immunologic research. Potential adverse effects of vaccines also require constant attention. These days vaccines are being tested as a way of limiting or reducing malignant tumors.

Immunotherapy is a more modern success story as biological agents such as monoclonal antibodies and receptor-blocking ligands are increasingly available for control of diseases due to immunological derangement.

The need for an Encyclopedia of Medical immunology is compelling. Our encyclopedia is divided for convenience into the four subject areas discussed above: Immune deficiency diseases, allergic diseases, autoimmune diseases and vaccines. Each of these areas has significant and immediate relevance to medical practice and public health. Each is a growing area of research.

By bringing together these different areas in one comprehensive publication, the encyclopedia illustrates and emphasizes the fundamentals of the immune response. For immunity to play its part in good health, it must maintain homeostasis within itself and with all other physiologic systems. The challenges to maintaining immunologic good health are both internal and external. In the face of changes in the environment, including climate, infectious agents and industrial exposures, human survival places a need for constant recalibration of the immune system. Internally, the effects of aging,

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hormonal changes, the microbiome and life cycle events (eg. puberty, pregnancy) also require readjustment of immunologic homeostasis. Interventions are designed to restore immunologic balance, to repair innate or induced deficiencies and to strengthen immune responses.

As Editors-in-Chief, we trust that the users will find this "encirclement" of a body of knowledge will prove helpful for decision making in promoting immunologic health and reducing immunologic disorders.

June 2014

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Preface

The rapid change in immunology is both exciting and intimidating. The number of papers identified as of April 2014, in PubMed by the search term "allergy" has increased 16,668 since January 2013 and by 4,084 since January 2014. How is anyone to stay abreast?

This volume of the Encyclopedia of Medical Immunology, "Allergic Diseases", has been assembled with the assistance of worldwide leading and emerging experts in the field of allergy and immunology. It is a living document as the growth of the science is much too rapid for textbooks to keep pace. The editors identified the major areas of allergic diseases that are likely to prompt questions and have engaged section editors to craft entries to answer these questions. Most of these are disease- or organ-focused, but others apply to general concepts, such as anaphylaxis, pharmacology, allergen immunotherapy, and insect allergy. The editors anticipate the addition of other sections and additional entries as this volume expands.

The value is that the extensive knowledge of allergy and allergic diseases is distilled into a compendium that is searchable. The breadth of clinical science and active research in the field is reflected in the volume's range of topics, from IgE to contact dermatitis, from allergen immunotherapy to asthma, from insect hypersensitivity to rhinitis.

The editors wish to thank the outstanding section editors and the authors of the individual submissions for saying "yes" when asked to participate in this initiative. This is a group effort, and they should receive the credit.

The editors are confident you will find this volume an excellent "go- to source" for questions related to allergic diseases and a useful reference that meets your immediate and future needs.

We acknowledge the invaluable efforts of Ms. Geeta Gehi and the publisher for their assistance in making this effort a success.

June 2014

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Photo credit:
Australian Academy of Science

Ian R. Mackay's research career, mostly directed to autoimmunity, began in 1956 in the Clinical Research Unit (CRU) of the Walter & Eliza Hall Institute and Royal Melbourne Hospital (RMH), Melbourne, Australia. It comprehended associations between disorders of immunological function and clinical expressions in diseases of obscure causation. Research laboratories in the Hall Institute and supervision of a 27-bed general medical ward in the adjacent RMH encouraged one to think of autoimmunity holistically rather than via any single disease. A particular interest in autoimmunity and liver and a collaboration with D Carleton Gajdusek pointed to autoimmune responses in causation of two major entities, chronic active hepatitis and primary biliary cirrhosis (PBC). The detection of autoimmune reactivity of a monoclonal plasma paraprotein was a key element in Burnet's formulation of the Clonal Selection Theory of Acquired Immunity. Mackay's later return to PBC in the molecular era (1980s) in research with M Eric Gershwin resulted in cloning and identification of the gene for the disease-associated "mitochondrial" autoantigen of PBC, the E2 subunit of pyruvate dehydrogenase complex (PDC-E2). In autoimmune hepatitis, levels in serum of transaminase enzymes were found to reflect ongoing hepatocellular damage, so providing a monitor of efficacy of immunosuppressive drugs prednisolone and azathioprine and, in the 1960s, the first long-term treatment

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trial established their benefit. This drug combination remains today as the standard therapy for autoimmune hepatitis.

In the early 1960s, Mackay became sufficiently convinced of the reality of autoimmunity to compile with F MacFarlane Burnet the first authoritative text (1963). Thereafter, he made research contributions on numerous autoimmune diseases, thyroiditis, multiple sclerosis, myasthenia gravis, pemphigus, and gastritis. With "Reg" Strickland, gastritis was separated into Type A (autoimmune) and Type B (later, bacterial) gastritis, foreshadowing bacterial infection in peptic ulcer disease. Mackay became a major protagonist for the early development of the specialty of Clinical Immunology and with Senga Whittingham laid out specifications for the practice of this specialty. In the 1980s, the RMH drew on the CRU to establish an AIDS service, and observations made on human papillomavirus (HPV) infection in rectal swabs of homosexual men led to Ian Frazer's development in Brisbane of an HPV vaccine for prevention of virus-induced cervical cancer.

In 1987, Mackay relocated to the Department of Biochemistry, Monash University, where with Merrill Rowley an autoimmunity laboratory was established for further investigation of PBC, Type 1 (autoimmune) diabetes, and rheumatoid arthritis. The laboratory sought to identify in various autoimmune diseases molecular epitopes (auto-epitopes) using contemporary techniques including antibody screening of phage-displayed random peptide libraries. A notable achievement arising from collaborations at Monash with James Whisstock, Gus Fenalti, and others was the crystallization of both isoforms of glutamic acid decarboxylase (GAD) 65 and 67, revealing the 3D structure and "molecular positioning" of the reactive antibody epitopes of the autoantigenic 65kD isoform and differences from the non-autoantigenic 67 kD isoform. This work is ongoing.

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Noel R. Rose received his basic training in microbiology at Yale University followed by PhD and MD degrees at the University of Pennsylvania and State University of New York at Buffalo. He was appointed to the faculty at Buffalo in 1951, where he began his research career. His early studies under the tutelage of Professor Ernest Witebsky searched properties of the organ-specific antigens that characterize the unique functions of normal and malignant cells. In the course of these investigations, he discovered that he could produce an autoimmune disease in the thyroid gland by immunization with the major thyroid protein thyroglobulin. Until that time, it was generally accepted that in only a few "privileged sites" in the body were such pathogenic autoimmune responses possible. These studies opened the modern era of research on the autoimmune diseases and set the direction of Rose's career since that time. In the 1960s, he investigated the requisite conditions for inducing autoimmune disease and the delineation of the basic immunologic and pathological processes. He included studies on other organs, such as the pancreas, as well as allergic diseases. In 1971, he and his colleagues discovered the first major gene that is responsible for susceptibility to autoimmune diseases and proved that it was a member of the major histocompatibility complex. At that time, he moved his laboratory to Wayne State University in Detroit, where he and his colleagues carried out detailed studies on the genes responsible for autoimmune disease of the thyroid gland. He also performed early experiments of the regulatory role of the thymus-derived lymphocytes and other studies related to unique enzymes of specialized cells, especially prostatic cancer. In 1981, Rose moved to Johns Hopkins University, where he created a department devoted to studies of immunity and infection. He directed much of his research to infectious agents and chemicals that induce autoimmune disease. A major effort was devoted to developing an experimental model of autoimmune heart disease produced in genetically prepared mice by infection with a virus that led work to the first identification of a well-defined antigen responsible for cardiac inflammation. Investigations on this model revealed a stepwise process that leads from infection to initial harmless autoimmunity to later life-threatening autoimmune disease.

In addition to his research, Rose has been deeply involved in the clinical practice of immunology. He directs a diagnostic immunology laboratory; he

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serves as expert consultant to the World Health Organization and as director of the WHO Collaborating Center for Autoimmune Disorders. He chaired the first committee on clinical immunology of the American Association of Immunologists and was co-founder of the Clinical Immunology Society. He was editor-in-chief of the first six volumes of the Manual of Clinical Immunology co-sponsored by the American Association of Immunologists and the American Society for Microbiology.

Throughout his career, Rose has had the opportunity of working with a number of leading investigators including Pierre Grabar at the Pasteuer Institute, Paris; Henry Isliker at the Swiss Institute for Cancer Research; Sir James Gowans at Oxford University; and Sir Gustav Nossal and Ian Mackay at the Walter and Eliza Hall Institute in Australia. While at the Hall Institute, Rose was invited to prepare a book describing the broad area of autoimmune disorders. He joined with Mackay in producing the first volume of the book, *The Autoimmune Diseases*, which is now in its fifth edition.

At Johns Hopkins, he continues to teach in medicine and public health and directs an active research laboratory. He also heads the Center for Autoimmune Disease Research, which facilitates communication and collaboration among specialists in the different facets of autoimmune disease research.

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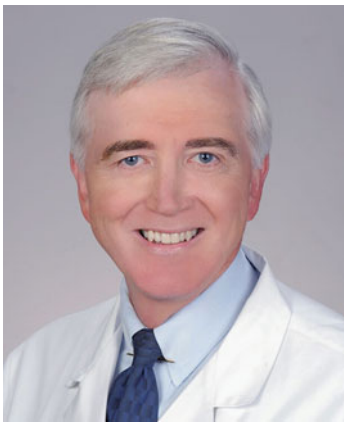

Dennis K. Ledford, MD Division of Allergy and Immunology, Department of Internal Medicine, University of South Florida Morsani College of Medicine, James A. Haley Veterans' Hospital, Tampa, FL, USA

Dennis K. Ledford was born and grew up in East Tennessee and was the valedictorian of his high school class.

He attended college at Georgia Institute of Technology, Atlanta, Georgia. He graduated magna cum laude with a degree in chemical engineering and was selected for membership in Tau Beta Pi, the engineering honor society. He received his medical degree from the University of Tennessee Health Science Center. Dr. Ledford is a member of Alpha Omega Alpha Honor Medical Society (AOA), being selected as a third year student at the University of Tennessee, and he received the outstanding student of medicine award, graduating first in his class. He remained in Memphis for the completion of his internal medicine residency and served as chief medical resident for Dr. Gene Stollerman at the City of Memphis Hospitals. A fellowship in rheumatology and immunology followed at New York University and Bellevue Hospital in New York. A fellowship in allergy and immunology at the University of South Florida completed his education. Dr. Ledford remained in Tampa at the University of South Florida (USF), joining the faculty and achieving the rank of professor of medicine in 2000. Dr. Ledford received the honor of being named the USF Morsani College of Medicine Mabel and Ellsworth Simmons Professor of Allergy in 2012. He is

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actively involved in the pediatric and internal medicine allergy/immunology training programs and established and was the prior program director of Clinical and Laboratory Immunology at the University of South Florida.

Dr. Ledford has contributed in a variety of areas to the USF Morsani College of Medicine. He is a current member of the Professionalism Committee and is a faculty member of the Professionalism Education Task Group. He is the Past President of the Medical Faculty and served as President from 2012 to 2013. He has served on the medical student selection committee and was chair of the committee for two separate terms. He is the current director of the USF Allergy and Immunology Clinic at the Morsani Center for Advanced Health Care.

Dr. Ledford received the outstanding teacher award from the USF medical house staff, the outstanding medical volunteer of the year award in Hillsborough County, and the Governors' Community Service Award from the American College of Chest Physicians. He has served on the American Board of Allergy and Immunology as secretary/treasurer and leader of the Maintenance of Certification initiative. He is a past president of the Florida Allergy, Asthma and Immunology Society, past member and vice-chair of the Residency Review Committee for Allergy/Immunology of the Accreditation Council of Graduate Medical Education, an associate editor of *The Journal of Allergy and Clinical Immunology*, editorial board member for *Annals of Allergy, Asthma and Immunology* and *The Journal of Allergy and Clinical Immunology: In Practice,* and a past contributing editor for *Allergy Watch*. He is a contributor to *UpToDate*.

Dr. Ledford has served the American Academy of Allergy, Asthma, and Immunology (AAAAI) in a number of capacities. He was a prior governor of the Southeast Region of the State, Local, and Regional Allergy Societies of the AAAAI and chair and member of several committees and currently serves on the In-Service Training Exam Committee as a section leader. He has been a member of the board of directors and was President of the AAAAI from 2011–2012. He served on numerous task forces for the AAAAI and as chair of the International Collaboration in Asthma Allergy and Immunology. Dr. Ledford is currently the chair of the Steering Committee for the Allergy, Asthma and Immunology Education and Research Trust.

Dr. Ledford works with the division's faculty in managing Academic Associates in Allergy, Asthma and Immunology and is chief of the section of allergy and immunology at Florida Hospital, Tampa. He has been selected as one of America's best doctors consecutively for more than 20 years. Clinical responsibilities occupy the majority of his time, but he has developed research interests in severe, steroid-dependent asthma, allergen characterization, the association of gastroesophageal reflux disease and upper airway disease, and eosinophilic esophagitis. Dr. Ledford has been the principal investigator in more than 20 and coinvestigator in more than 160 clinical trials, authoring or coauthoring more than 120 publications. He has been married to Jennifer S. Ledford for 40 years and is blessed with three children, Keith, Michael, and Robert, and 10 grandchildren, Madelyn, Andrew, Isaiah, Ian, Lukas, Kaila, Annika, Grant, Ethan, and Miles.

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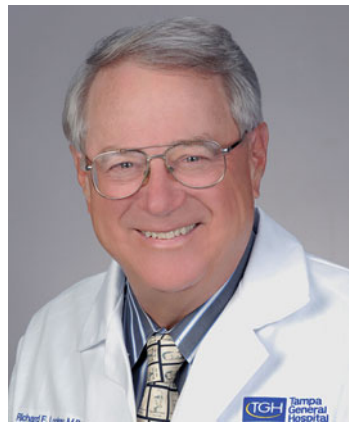

Richard F. Lockey, MD, MS Division of Allergy and Immunology, Department of Internal Medicine, University of South Florida Morsani College of Medicine, James A. Haley Veterans' Hospital, Tampa, FL, USA

Richard F. Lockey director of the Division of Allergy and Immunology, Department of Internal Medicine, and professor of medicine, pediatrics, and public health, was named the Joy McCann Culverhouse Chair in Allergy and Immunology at the University of South Florida College of Medicine, Tampa, Florida, in 1997. He is a tenured physician at the University of South Florida Morsani College of Medicine's Health Science Center. He is also the chief of the Section of Allergy and Immunology at the James A. Haley Veterans' Hospital. In 2007, he was honored by receiving the additional title of University Distinguished Health Professor.

He joined the faculty of the University of South Florida College of Medicine in 1973, at which time he also became a staff member at the James A. Haley Veterans' Hospital. He is board-certified in internal medicine and in allergy and immunology.

The Division of Allergy and Immunology, Department of Internal Medicine, is a widely recognized treatment, teaching, and research facility in the field of allergy, asthma, and clinical immunology. For example, in one publication, five clinicians named "best doctors" in America are members of the Division. Through the efforts of Dr. Lockey, the Division is endowed with more than US$14 million dedicated to teaching and research. The faculty in the Division work in the state-of-the-art Joy McCann Culverhouse Airway Disease Research Center, a molecular biology laboratory with three full-time basic scientists devoted to long-term treatments and even a cure for allergic and immunologic diseases and asthma. In addition, the Division's Clinical Research Unit has participated in most of the major drug innovations for the treatment of allergic diseases and asthma over the past 40 years. The Division currently has approximately 50 members including six core clinical physicians, three PhDs, eight voluntary clinical faculty, and other healthcare professionals and support staff. It is closely associated with and collaborates in teaching, research, and clinical care with the Division of Allergy and

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Immunology, Department of Pediatrics, at the University of South Florida College of Medicine, Tampa, Florida, and All Children's Hospital, St. Petersburg, Florida.

Dr. Lockey received an undergraduate degree from Haverford College, Haverford, Pennsylvania, and a medical degree from Temple University School of Medicine, Philadelphia, Pennsylvania, where he was a member of the Alpha Omega Alpha National Medical Honor Society. After completing his internship in medicine at Temple University School of Medicine in 1966, he finished his residency in internal medicine in December 1968 and fellowship in allergy and immunology at the University of Michigan, Ann Arbor, Michigan, in December 1970, where he also attended the University of Michigan Rackham Graduate School and received a master's degree in internal medicine. He was a major, U.S. Air Force, and served as chief of allergy and immunology at Carswell Air Force Base, Fort Worth, Texas, from 1970 to 1972.

Dr. Lockey has authored, coauthored, or edited over 650 publications including 14 books, 20 monographs, and numerous experimental papers, invited papers, editorials, and book chapters. He has been an invited speaker on more than 450 occasions for both national and international scientific conferences. He is a coeditor of *The Journal of Investigational Allergology and Clinical Immunology* and is on or has served on the editorial boards of a variety of peer-reviewed journals including *The Journal of Allergy and Clinical Immunology*. In 1987, he edited a special edition of *The Journal of the American Medical Association*, *Primer on Allergic and Immunologic Diseases*. He was a coeditor of the first American College of Physicians and American Academy of Allergy, Asthma, and Immunology *Medical Knowledge Self-Assessment Program (MKSAP) in Allergy and Immunology* published in 1992. He has published and coauthored articles in *Nature*, *JAMA*, and *The New England Journal of Medicine*.

Fellowships include the American Academy of Allergy Asthma and Immunology, the American College of Chest Physicians, and past fellow, American College of Physicians. He is also a member of the American Thoracic Society, European Academy of Allergology and Clinical Immunology, Clinical Immunology Society, American College of Occupational and Environmental Medicine, as well as the European Thoracic Society. He is a past member of the American Medical Association and is a current member of the Florida Allergy, Asthma, and Clinical Immunology Society.

Other professional honors include serving as president of the American Academy of Allergy, Asthma, and Immunology (1992–1993). Dr. Lockey is also a past Director of the American Board of Allergy and Immunology, the organization that oversees and examines physician candidates for certification as specialists in allergy/immunology. He was elected to the board of the World Allergy Organization in 1995 and served as its president from January 2010 until December 2012. Dr. Lockey has served as an associate on two World Health Organization (WHO) committees striving to promote the highest level of health for all people globally. Each committee has prepared a vital position paper. One document was entitled *Prevention of Allergies and Asthma* and the other *Allergic Rhinitis and Its Impact on Asthma*. He was

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also a coeditor of a third project, the WHO position paper *Allergen Immunotherapy: Therapeutic Vaccines for Allergic Disease*s published in 1998. He was editor of the World Allergy Organization's web page and the World Allergy Organization's e-mail *News and Notes from 2004–2009,* which serves all physicians, particularly physicians in the specialty of allergy and immunology, throughout the world.

In 1992, Dr. Lockey received a "Certificate of Appreciation" from the Florida Medical Association in addition to being featured with Drs. Samuel C. Bukantz and Robert A. Good, mentors and colleagues, on the cover of the June/July 1996 special issue of *The Journal of the Florida Medical Association*.

Included among the numerous distinctions Dr. Lockey has received throughout his career are the Alumni Achievement Awards, Temple University School of Medicine, Philadelphia, PA, and McCaskey High School, Lancaster, PA. He has also received an award for Outstanding Leadership in Chapter Development and Patient Support from the National Asthma and Allergy Foundation of America, an appreciation award from the Asthma and Allergy Foundation of America, Florida Chapter, and the Team Physician Award for his services as a volunteer physician for the University of South Florida Athletics Department. He received a Special Recognition Award in 1993 and Distinguished Service Award in 1999 from the American Academy of Allergy, Asthma, and Immunology. In 2008, he was awarded the Distinguished Clinician Award from this same organization. He was awarded the Florida Academy of Sciences Medal for the year 2000 presented for outstanding work in scientific research, activities in the dissemination of scientific knowledge, and service to the community. He received the University of South Florida Distinguished Service Award in 2001 and is an honorary member of several societies. He was awarded the Southern Medical Association, Dr. Robert D. and Alma W. Moreton Original Research Award in 2012.

As Director of the Division of Allergy and Immunology, Dr. Lockey has helped train over 90 MDs in the specialty program of allergy and immunology and approximately 40 postgraduate PhDs or MDs from various parts of the world in clinical and basic research. Dr. Lockey continues to spend equal amounts of time caring for patients in basic and clinical research, particularly as it relates to allergic and immunologic diseases, and teaching at the University of South Florida College of Medicine and its affiliated hospitals. Dr. Lockey is married to Carol Lockey and has two children, Brian Christopher Lockey and Keith Edward Lockey, and is blessed with four grandchildren, Olivia, Benjamin, William, and Nicholas.

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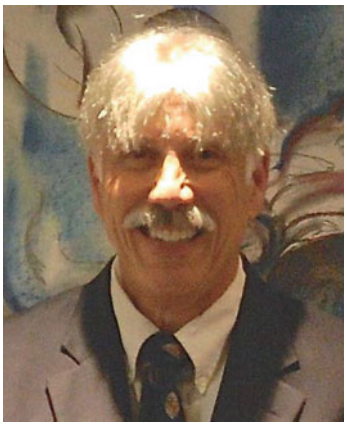

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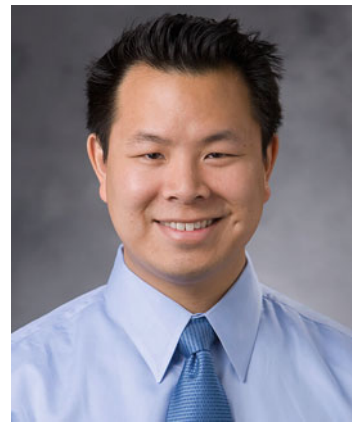

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A

Activating and Inhibitory Receptors on Mast Cells

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Synonyms

Allergy; Cell activation; Cell signaling; Inflammation; Mast cells; Regulation

Definition

Cell activation results from the transient displacement of a balance of positive and negative signals that are constitutively generated in resting cells. This physiological balance can be displaced when cell surface receptors are engaged by extracellular ligands. Mast cells express a variety of membrane receptors that control the biological responses of these cells. These include activating receptors and inhibitory receptors.

Activating receptors positively regulate biological responses of mast cells. Receptors for the Fc portion of immunoglobulins (FcR) such as high-affinity IgE receptors (FcεRI) trigger an array of secretory responses including the exocytosis of preformed mediators, the generation of arachidonic acid–derived eicosanoids, and the secretion of cytokines, chemokines, and growth factors. FcεRI do not trigger proliferative signals. Conversely, cytokine or growth factor receptors, such as Interleukin-3 receptors (IL-3R) or the Stem Cell Factor (SCF) receptor Kit, induce mast cell proliferation. They trigger no or minimal activation signals. Inhibitory receptors negatively regulate biological responses induced by activating receptors.

Activating and Inhibitory Receptors

Activating and inhibitory receptors trigger signals when they are engaged by specific extracellular ligands. Except G Protein–Coupled Receptors (GPCRs) that can trigger signals when binding monovalent ligands, most receptors trigger signals when aggregated by plurivalent ligands. Ligands with several identical binding sites or made of complexes of several identical molecules aggregate identical receptors on the same cell. This *homo-aggregation* applies to most activating receptors. Thus, FcεRI are aggregated when a multivalent antigen binds to receptor-bound IgE. Because mast cells co-express several receptors and because many extracellular ligands consist of complexes of different molecules, different receptors may be co-engaged by a single ligand.

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This *hetero-aggregation* may apply to different activating receptors or to activating and inhibitory receptors. In the first case, positive signals generated by activating receptors can synergize. In the second case, negative signals generated by inhibitory receptors antagonize with positive signals generated by activating receptors.

Activating receptors generate not only activation signals, but also inhibition signals. This can be unraveled by monitoring the release of granular mediators by mast cells sensitized with a constant amount of IgE antibodies and challenged with increasing concentrations of specific antigen. Mediator release dose-dependently increases up to an optimal concentration of antigen. Beyond this concentration, mediator release declines progressively and, in large excess of antigen, it is abrogated. This long-known bell-shaped dose–response curve was recently demonstrated to result from an active *auto-inhibition* of activating receptor signaling that limits mast cell activation beyond a given threshold (Huber 2013).

Inhibitory receptors generate inhibition signals only. They however need to cooperate with activating receptors in order to inhibit mast cell activation. Such cooperation is possible when extracellular ligands co-engage the two types of receptors on the same cell. IgG immune complexes, which can bind to FcεRI-bound IgE antibodies via the antigen moiety and to the inhibitory low-affinity IgG receptors FcγRIIB via the Fc portions of IgG antibodies, are such ligands. Activating and inhibitory receptors that are co-expressed by mast cells may have different specificities, such as FcεRI and FcγRIIB. Others, such as PIR-A and PIR-B, have the same specificity. They present themselves as pairs of activating and inhibitory receptors that are co-engaged by the same ligands.

Signaling Mechanisms Used by Activating Receptors

Signal Transduction by Activating Receptors

Signal transduction is the transformation of a mechanical perturbation, generated at the extracellular side of the plasma membrane, into a chemical perturbation, generated at the intracellular side of the membrane. The extracellular mechanical perturbation can be either a conformational change or the formation of receptor aggregates. The degree of aggregation depends on receptors and ligands. Kit and IL-3R are dimerized by SCF and IL-3, respectively. FcεRI are generally aggregated by multivalent antigens when these bind to receptor-bound IgE. In the vast majority of cases, the intracellular chemical perturbation is a phosphorylation event that is made possible because receptor aggregation brings close to each other protein kinases and their substrates. The kinases and their substrates depend on the type of receptors involved.

Growth factor receptors such as Kit are themselves tyrosine kinases, hence their generic name *Receptor Tyrosine Kinases* (RTKs). Their intracytoplasmic domain contains both the enzyme, i.e., a tyrosine kinase catalytic domain, and its substrates i.e., multiple tyrosines that become phosphorylated by a *trans-phosphorylation* process when RTKs are dimerized by growth factors (Lemmon and Schlessinger 2010).

Activating FcRs contain *Immunoreceptor Tyrosine–based Activation Motifs* (ITAMs) that are phosphorylated by src family tyrosine kinases. These enzymes are especially abundant in sphingolipid-/cholesterol-rich membrane microdomains into which engaged receptors transiently translocate. When phosphorylated, ITAMs recruit molecules that possess Src Homology 2 (SH2) domain(s). SH2 domains have an affinity for specific tyrosyl-phosphorylated molecules, among which are cytosolic tyrosine kinases and adapter molecules (Siraganian 2003).

Other activating receptors, such as the SLAM family member 2B4, contain several *Immunoreceptor Tyrosine–based Switch Motifs* (ITSMs), which, when phosphorylated, recruit SAP, an adapter molecule consisting of one SH2 domain (Veillette 2010).

The engagement of Toll-like receptors (TLRs) enables the recruitment of adapter molecules, such as Myd88 and/or TRIF, which recruit the protein kinases IRAK and TBK1, respectively (Sandig and Bulfone-Paus 2012).

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The engagement of cytokine receptors triggers the phosphorylation of transcription factors of the Signal Transducer and Activator of Transcription (STAT) family by Janus kinases (Jak) that are activated upon cytokine binding (Ihle et al. 1995).

Ligand binding triggers conformational changes of the heterotrimeric G Protein–coupled Receptors. This enables guanosine diphosphate (GDP), with which inactive receptors are associated, to be exchanged for guanosine trisphosphate (GTP), with which activated receptors are associated. Further signal transduction depends on the type of G protein (Hur and Kim 2002).

Glycosylphosphatidylinositol (GPI)-anchored receptors have no intracytoplasmic domain. They, however, concur to cell signaling by trapping activating receptors in src kinase–rich lipid microdomains where they reside, or by engaging activating receptors through interactions with their extracellular domains (Suzuki et al. 2007).

Generation of Signalosomes and Intracellular Propagation of Activation Signals

Whatever the receptors and the mechanisms by which initial signals were transduced, proximal signaling events enable the constitution of intracellular *signalosomes* that build up on scaffold proteins and in which signaling molecules are spatiotemporally organized. Molecules that are recruited and activated in signalosomes launch metabolic pathways, which ensure the intracellular propagation of signals from the membrane to the nucleus.

These pathways lead to the generation of phopshatidylinositol-3,4,5-trisphosphate [PI(3,4,5)P3] by phosphatidylinositol-3-kinase (PI3K) and the subsequent membrane translocation of signaling molecules that have a Plextrin Homology domain, to the activation of various types of Protein Kinases (PKA, PKC, etc.) and the subsequent activation of factors which, like NF-κB, control transcription, to the activation of small GTPases of the Ras, Rac, and Rho families and the subsequent activation of Mitogen-Activated Protein (MAP) kinases, to an increased concentration of intracellular Ca^{2+} and the subsequent activation of Ca^{2+}-dependent enzymes. Ultimately, these pathways end by the nuclear translocation of a variety of transcription factors and the subsequent transcription of cytokine genes.

Most intracellular pathways that lead to gene transcription are shared by the various activating receptors. The nature of biological responses of the cell depends on combinations of transcriptional events that control the expression of genes that encode secretory products or molecules, such as cyclins, that control the cell cycle and, ultimately, cell proliferation. As a consequence, pathways that are activated simultaneously by different receptors can merge and/or interfere with each others. The integration of signals generated by different activating receptors generally leads to an amplification of activating signals whereas the integration of signals generated by activating and inhibitory receptors leads to the negative regulation of activation signals (Bezbradica and Medzhitov 2012).

Signaling Mechanisms Used by Inhibitory Receptors

ITIM-Containing Inhibitory Receptors

The vast majority of inhibitory receptors contain one or several *Immunoreceptor Tyrosine–based Inhibition Motifs* (ITIMs) (Daëron et al. 2008). A hallmark of ITIM-containing molecules is that they become tyrosyl-phosphorylated, which enables them to recruit SH2 domain–containing phosphatases that inhibit cell activation. SH2 domain–containing phosphatases are indeed the intracellular effectors of negative signaling by ITIM-containing receptors. Depending on the receptor and on the phosphatase, the mechanisms of ITIM phosphorylation, the mechanism of phosphatase recruitment, and the consequences of this recruitment differ.

Four SH2 domain–containing phosphatases have been identified: the two lipid phosphatases SHIP1 and SHIP2 and the two tyrosine phosphatases SHP-1 and SHP-2. ITIM-containing receptors recruit either SHIP1/2 or SHP-1/2. Both types of inhibitory receptors require to be co-engaged with activating receptors to inhibit, but for different reasons: Coaggregation brings

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tyrosine kinases close to their substrates in the first case, whereas it brings tyrosine phosphatases close to their substrates in the second case.

FcγRIIB is the only *bona fide* ITIM-containing receptor that recruits SHIP1/2. These phosphatidylinositol-5-phosphatases have indeed an affinity for the phosphorylated FcγRIIB ITIM, but not for those of most other ITIM-containing inhibitory receptors. Also, FcγRIIB, which has a single ITIM, cannot recruit the two-SH2 domain–containing SHP-1/2. FcγRIIB aggregation does not lead to ITIM phosphorylation. The coaggregation of FcγRIIB with activating receptors does. Coaggregation indeed enables Src kinases that associate with activating receptors to phosphorylate also the ITIM in the inhibitory receptor. As a consequence, FcγRIIB-dependent negative regulation does not operate in resting cells. It only operates when activation has been launched. Once recruited by phosphorylated, FcγRIIB, SHIP1 can inhibit activation signals by at least two mechanisms. One depends on its enzymatic activity; the other does not. SHIP1 hydrolyzes the 5-phosphate group in the inositol ring of PI(3,4,5)P3, preventing thus PI(3,4,5)P3-dependent recruitment of critical signaling molecules. When phosphorylated, SHIP1 recruits a cytosolic adapter that recruits rasGAP, which inhibits Ras activation and, ultimately, prevents the transcription of cytokine genes.

Other ITIM-containing receptors, i.e., most inhibitory receptors, have more than one ITIM and they use the two-SH2 domain–containing tyrosine phosphatases to inhibit cell activation. Unlike FcγRIIB, these receptors are constitutively associated with Src family tyrosine kinases. Their phosphorylation therefore requires that they are aggregated, but not that they are co-aggregated with activating receptors. When tyrosyl-phosphorylated, they recruit SHP-1/2, but not SHIP1/2. Coaggregation is necessary for these molecules to inhibit cell activation. Indeed, SHP-1/2 need to be brought close to their phosphorylated substrates for being able to act on them. The substrates of SHP-1 and/or SHP-2 include molecules that are present in the signalosome and whose phosphorylation is critical for both proximal and distal activation signals.

Inhibitory Receptors That Do Not Contain ITIM

Some receptors can use ITIM-independent mechanisms to negatively regulate mast cell activation. One of the ITSM of 2B4 can recruit various molecules involved in negative signaling. The OX-2 glycoprotein receptor CD200R contains no ITIM but a tyrosine-rich region which, upon phosphorylation, can recruit SHIP1 via the recruitment of Dok1/2. G Protein–coupled receptors that activate adenylate cyclase, such as the adenosine receptors A2a and A2b and the PGE2 receptor EP2, can inhibit mast cell activation by increasing the intracellular levels of cyclic AMP. When engaged by the filarial protein ES-62, TLR-4 sequesters Protein Kinase Cα and inhibits FcεRI signaling. Transforming Growth Factor β downregulates FcεRI expression by inhibiting the synthesis of FcεRIα, FcRγ, and FcRβ at the translational level. The member of the *TIR domain–containing superfamily of TLR family and IL-1 receptors*, IL-33 receptor (aka ST2), inhibits IL-4R signaling by interacting with the adapters MyD88 and Mal.

Activating and Inhibitory Receptors Expressed By Mast Cells

Activating Receptors

Activating receptors expressed by mast cells are listed in Table 1 (Migalovich-Sheikhet et al. 2012; Gilfillan and Tkaczyk 2006). They belong to several families of receptors: the Immunoglobulin Superfamily (IgSF), the GPCR family, Cytokine receptors, TLR, and GPI-linked receptors.

IgSF receptors comprise RTK that by themselves possess a tyrosine kinase domain and ITAM- or ITSM-containing receptors that recruit tyrosine kinases. Mast cell RTKs include receptors for growth factors such as SCF and Vascular-Endothelial Growth Factor. They promote mast cell proliferation. ITAM-containing receptors expressed by mast cells are receptors for the Fc portion of antibodies. They include the high-affinity IgE receptors FcεRI and the low-affinity IgG receptors FcγRIIA in humans and FcγRIIIA in mice. The high-affinity IgG receptors FcγRI

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Activating and Inhibitory Receptors on Mast Cells, Table 1 Activating receptors expressed by mast cells

Ligands		IgSF Receptors		7TM GPCR	Cytokine receptors	Toll-like receptors	GPI-anch. receptors
		RTK	Immunoreceptors				
Growth Factors	*SCF*	Kit					
	VEGF	VEGF R					
Antibodies	*IgE*		FcεRI				
	IgG		FcγRIIA (h), FcγRIIIA (m)				
Chemokines	*CXCL, CCL*			CXCR1-4 CX3CR1 CCR3-5 CCR1			
Lipid Mediators	*LT*			LT R			
	PAF			PAF R			
	PGE2			EP3			
Amines	*Histamine*			H1-4R			
	Serotonin			5HTR			
Sphingosine P				S1P-R1/2			
Adenosine				A1, A3			
Neuropeptides	*Subst. P*			NK1R			
Anaphylatoxins	*C3a/C5a*			C3a R/C5a R			
Leucotrienes				CysLT1/2			
Endothelins	*ET-1-3*			ETA, ETB			
Corticotropin	*CRF*			CRH R			
Cytokines	*IL-3-5*				IL-3 R IL-4 R IL-5 R		
	TSLP				TSLP R/IL-7 R		
Microb. Prod.	*endotoxins*					TLR2/TLR4	
	uPA						uPA R
Bacteria, 2B4							CD48

can be induced by IFN-γ in human but not in mouse mast cells. Whatever their specificity, these FcR trigger mast cell activation when engaged by antibodies and antigen. ITSM-containing receptors are the SLAM family member 2B4 that can be engaged either by 2B4 through homotypic aggregation, or by other SLAM family members through heterotypic aggregation, on the same or on different membranes.

A heterogeneous group of GPCR comprises receptors for chemokines, lipid mediators, vasoactive amines, sphingosine phosphate, adenosine, neuropeptides, and anaphylatoxins. Most of these receptors can induce mast cell secretion. Some, like leukotriene receptors, induce mast cell proliferation. Others, like chemokine receptors, trigger mast cell chemotaxis. They thus mediate the recruitment of mast cells in inflammatory sites. Endothelins are a family of vasoactive peptides that can both be produced by mast cells and activate mast cells through the endothelin receptors ET_A. Mast cells, however, also produce proteases that degrade endothelins.

Mast cell cytokine receptors include IL-3R, IL-4R, IL-5R, and TSLP/IL-7R. They trigger mast cell differentiation and proliferation. Toll-like receptors such as TLR-2 and TLR-4 induce mast cell to secrete cytokines but not to degranulate when engaged by endotoxins or other bacterial products.

Several GPI-anchored receptors have been reported to trigger mast cell responses. Thus, the urokinase-type plasminogen activator receptor (uPAR, CD87) induces human mast cell chemotaxis. Various bacteria bind to CD48 and trigger phagocytosis and cytokine secretion. CD48 can also be engaged by 2B4, a member of the SLAM

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family that is co-expressed by mast cells, and trigger cell activation.

Activating receptors can also generate negative signals that inhibit mast cell activation. FcεRI signaling is regulated by SHIP1 in the absence of inhibitory receptor engagement (Huber 2013). IgE-induced secretory responses are markedly enhanced in SHIP1$^{-/-}$ mast cells, and SHIP1 is dose-dependently tyrosyl-phosphorylated when FcεRI-bound IgE are engaged by increasing concentrations of antigen in wild-type mast cells. The mechanism by which FcεRI recruits SHIP1 in this auto-regulation is unclear. Likewise, 2B4 can activate mast cells when engaged by members of the CD2 family such as CD48. 2B4, however, also generates inhibitory signals. 2B4 indeed contains four ITSM, three of which recruit molecules that concur to cell activation whereas one of them recruits SHP-1/2, SHIP1, and Csk that inhibit cell activation (Veillette 2010).

Inhibitory Receptors

Inhibitory receptors expressed by mast cells are listed in Table 2 (Migalovich-Sheikhet et al. 2012). Three groups of receptors can be distinguished: ITIM-containing inhibitory receptors that use the lipid phosphatases SHIP1/2, ITIM-containing inhibitory receptor that use the protein phosphatases SHP-1/2, and inhibitory receptors that have no ITIM (Daëron et al. 2008).

FcγRIIB are the only ITIM-containing receptors that recruit SHIP1/2. The co-engagement of FcγRIIB with FcεRI or with FcγRIIIA by antigen-antibody complexes on mouse mast cells dramatically inhibits all IgE- or IgG-induced responses (Daëron et al. 1995). The co-engagement of FcγRIIB with Kit inhibits SCF-induced mouse mast cell proliferation (Malbec et al. 1999). Although high amounts of FcγRIIB that have a major dominant inhibitory effect on IgG- and IgE-induced activation were found in human basophils, FcγRIIB expression is questionable on human mast cells. It may differ markedly on mast cells from different tissues. Human cord blood-derived mast cells were indeed reported to express FcγRIIB, but not skin-derived human mast cells.

The co-engagement of FcεRI with all other ITIM-containing receptors also inhibits mast cell activation. These inhibitory receptors include Siglec, which binds to sialic acid, SIRPα, which binds to the widely expressed CD47, the MCH class I receptors PIR-B, ILT/LIR and NKG2A, PECAM-1, which aggregates with itself, LAIR-1, which binds to collagen, CD72, which binds to CD5, gp49B1, which binds to integrins, CD300/MAIR, which binds to phosphatidyl serine, phosphatidyl ethanolamine, and ceramides on dead cells, and Allergin-1, whose ligands are unknown. All these receptors contain more than one ITIM. This enables them to recruit the two-SH2 domain–containing tyrosine phosphatases SHP-1 and/or 2.

Inhibitory receptors with no ITIM include receptors for cytokines, such as the IL-10R and the IL-33 receptor ST2, the transforming growth factor TGFβ receptor1, the adenosine receptors A2a and A2b, the prostaglandin E2 receptor EP2, CD200R that binds to the glycoprotein OX-2 (CD200), expressed by a broad range of tissues including lymphoid cells, neurons, and endothelium, and TLR-4, which inhibits FcεRI signaling when engaged by the filarial protein ES-62.

Mast Cell Receptors in Health and Disease

Inflammation is a physiological defense mechanism. It involves the many myeloid cells that function as the cellular effectors of innate and adaptive immune responses. Mast cells are among these cells. These can be activated by microbial products and by a variety of other molecules in innate immunity or by molecular effectors of adaptive immunity via cytokine, chemokine, and Fc receptors (Newton and Dixit 2012). Normally, inflammation is tightly controlled and remains unapparent. It can be pathogenic if it escapes from regulation. Autoimmunity and allergy are examples of pathological inflammation generated by not properly controlled immune responses. Mast cells have been implicated in both conditions. A well-controlled balance between activating and inhibitory

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Activating and Inhibitory Receptors on Mast Cells, Table 2 Inhibitory receptors expressed by mast cells

	ITIM-containing Receptors		
Ligands	*SHIP1/2*	*SHP-1/2*	Non ITIM Receptors
IgG immune complexes	FcγRIIB		
Sialic acid		Siglec	
Ph.serine/ethanolamine; ceramides		MAIR-I /CD300	
CD47		SIRPα	
MHC-I		PIRB	
MHC-I (HLA-G)		ILT/LIRs	
MHC-I (HLA-E)		NKG2A /CD94	
PECAM-1		PECAM-1	
Collagen		LAIR-1/CD305	
CD5		CD72	
integrin α(v)β3		gp49B1	
?		Allergin-1	
Microbial products			TLR4
OX-2			CD200R1
*TGF*β			TGFβ-R1
PGE2			EP2
Adenosine			A2a, A2b
IL-10			IL-10R
IL-33			ST2/IL1RL1

receptors therefore determines whether mast cells contribute to protective immunity or to pathogenic immunity (Gilfillan and Beaven 2011). Human mast cells, however, were involved in various pathological processes (Bischoff 2007).

Mast Cell Receptors in Protective Processes

Although they are mostly known for their pathogenic properties, mast cells have been increasingly recognized to have protective roles. Several mast cell TLRs are involved in the protection against microorganisms, as mast cell–deficient mice were markedly more sensitive to infection by several pathogens, especially Gram-negative bacteria. This protection primarily depends on TLR-induced TNF-α secretion. Interestingly, nematodes that express ES62, a protein produced by parasitic roundworms, were reported to modulate mast cell–dependent inflammation. Mast cells were found to protect from honeybee, snake, lizard, and scorpion venoms. Venoms indeed induce mast cell degranulation via the endothelin receptor ET_A and they are degraded by proteases contained in granules released by activated mast cells. Urokinase can protect from bronchial obstruction by promoting fibrinolysis through mast cell urokinase-type plasminogen activator receptors. As it binds to lipids expressed by the membrane of dead cells, CD300/MAIR has been proposed to contribute to the removal of apoptotic cells.

Mast Cell Receptors in Pathogenic Processes

Activating receptors expressed by mast cells have been involved in pathological mast cell proliferations, chronic inflammation, anaphylaxis, allergy (Galli and Tsai 2012), and autoimmunity.

Kit is essential for mast cell proliferation and differentiation, particularly into serosal-type mast cells. Gain-of-function mutations of Kit are responsible for the uncontrolled proliferation of mast cells in mastocytosis and mastocytomas (Gotlib et al. 2013).

Inflammation involves the attraction of numerous cells at inflammatory sites. Altogether, chemokine receptors attract mast cells by stimulating chemotaxis in response to a variety of chemoattractants. By acting on mast cell purinergic receptors, adenosine present in extracellular fluid contributes to asthma symptoms. Adenosine indeed provokes a mast-cell-dependent bronchoconstriction in asthmatic and chronic obstructive pulmonary disease patients (Rudich et al. 2012). Corticotropin-releasing

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hormone receptors are thought to account for stress-induced inflammation and stress-enhanced allergic reactions. The engagement of neuropeptide receptors by substance P activates human skin mast cells and are involved in the pathogenesis of urticaria (Nakamura et al. 2009).

Anaphylaxis is a hyperacute systemic allergic reaction. IgE-induced, FcεRI-dependent mast cell activation accounts for IgE-induced passive anaphylaxis, and it is well known to initiate allergic reactions. IgG antibodies, however, are also potent inducers of anaphylaxis (Jonsson and Daëron 2012). Both types of reaction are dampened by FcγRIIB. Likewise, gp49B1 protects from anaphylaxis. gp49B1-deficient mice indeed exhibited enhanced IgE-induced anaphylactic shocks. The recently described ITIM-containing receptors of the CD300 family were found to act as potent negative regulators of anaphylaxis and of other FcεRI-dependent allergic reactions (Borrego 2013). By enhancing IgE-induced mast cell activation, Platelet-Activating Factor (PAF) can aggravate allergic reactions. By activating airway mast cells directly, it can contribute to bronchospasm in anaphylaxis. PAF plasma levels are increased in patients undergoing anaphylaxis. The anaphylatoxins C3a and C5a are generated during anaphylaxis, and the level of C3a correlates with the severity of the shock. C5a, but not C3a, behaves as a skin mast cell secretagogue in humans (Schafer et al. 2013). Sphingosine receptors are likely to be involved in anaphylaxis as their blockade reduced circulating histamine levels in mast cell–dependent mouse anaphylaxis. Serotonin receptors expressed by human mast cells were involved in allergic contact eczema, atopic eczema, and psoriasis. Finally, histamine can activate mast cells via H4-R and induce leukotriene B4 secretion. Mast cells, however, also express H2-R through which histamine can inhibit mast cell activation. The interplay between these two receptors can therefore control the effects of histamine on mast cells.

Mast cells have been involved in several systemic autoimmune diseases that depend on autoantibodies (Sayed et al. 2008). The engagement of IgG receptors that have antagonistic properties may critically determine the clinical outcome. Thus, the reconstitution of mast cell–deficient mice with mast cells from mice lacking activating FcγR failed to restore experimental encephalomyelitis, while reconstitution by mast cells from FcγRIIB-deficient mice enhanced the disease.

Mast Cell Receptors in Therapeutics

The many pathological processes in which mast cell receptors are involved make them potential targets/tools in therapeutics for a variety of diseases. Conceivably, one can aim at dampening activation signals whose excess causes mast cell–dependent pathological effects and/or at enhancing inhibition signals that insufficiently control mast cell activation. Conversely, one can aim at enhancing activation signals involved in mast cell–dependent protective processes and/or at dampening inhibitory signals. One can therefore imagine all kinds of theoretical interventions that could have beneficial effects in disease. Below are mentioned only examples of therapeutic approaches that have been used in the clinics or, at least, the proof of concept of which has been demonstrated in animal models. These treatments comprise chemical inhibitors of receptor signaling, natural ligands of mast cell receptors, antibodies against receptors, whether used as antagonists or as agonists, antibodies against receptor ligands, and bispecific molecules that co-engage different receptors. Symptomatic treatments that aim at inhibiting the pharmacological effects of mast cell mediators by targeting corresponding receptors on other cell types are not considered here.

As it is caused by an uncontrolled Kit activation, clinical trials based on the use of tyrosine kinase inhibitors have been conducted in mastocytosis patients. Globally, the results have not met expectations. Possible reasons are that multiple Kit mutations have been found in mastocytosis, all of which may not be sensitive to inhibitors. A small molecule that inhibits Syk was found to inhibit IgE-induced mouse mast cell activation in vitro and, when administered orally, experimental anaphylaxis in vivo. Allergen-driven symptoms were reduced in allergic rhinitic patients exposed to pollen following intranasal dosing of a Syk inhibitor. Antihistamine receptors have long been used in allergy.

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Although they probably also act on mast cell receptors, their therapeutic effect likely depends more on their action on histamine receptors expressed by the many cells involved in allergic inflammation.

An example of the use of natural ligands of mast cell receptors in therapeutics is the thrombolytic effects of low-doses of urokinase that has been proposed to treat patients with massive pulmonary emboli. Here again, the action of the drug on mast cells is likely to be a minor contribution to the therapeutic effect.

The best example of an efficient therapeutic antibody that targets a ligand of mast cell receptors is anti-IgE. This humanized monoclonal anti-human IgE is directed against an epitope located in the binding site of IgE that interacts with FcεRI. It was conceived as a means to prevent the binding of antibodies to IgE receptors on mast cells. It turned out to act differently. It was indeed found to remove most of plasma IgE, leading to a dramatic downregulation of FcεRI expressed by mast cells and other cells. Receptor occupancy by IgE indeed markedly increases the FcεRI half-life on the cell membranes. Consequently, in the absence of IgE, unoccupied FcεRI are rapidly degraded and they are virtually removed from the surface of mast cells and basophils. More than 10 years of use proved anti-IgE antibodies to be an efficient treatment of several allergic conditions associated with low to moderately elevated IgE levels.

Antibodies can be used as agonists rather than as blockers. Thus, antibodies directed against the inhibitory receptor CD200R before antigen challenge were reported to inhibit experimental Passive Cutaneous Anaphylaxis in mice and macaques.

Finally, attempts have been made to use bispecific molecules that co-engage FcεRI with inhibitory receptors. Three types of molecules have been used to co-engage FcεRI with FcγRIIB. One was a genetically engineered fusion molecule made of the C-terminal domains of a human IgE and the C-terminal domains of a human IgG1. Another was a fusion protein made of a major cat allergen and the C-terminal domain of a human IgG1. A third molecule was made by chemically coupling a Fab fragment from an anti-IgE antibody directed against an epitope outside of the binding site to FcεRI (hence accessible on FcεRI-bound IgE) and a Fab fragment of an anti-human FcγRII. Proof of concept validation was obtained for the three molecules in experimental models. A similar approach was attempted that aimed at co-engaging FcεRI with CD300/MAIR. A bispecific antibody fragment linking CD300a to FcεRI-bound IgE abolished IgE dependent PCA and antigen-induced acute experimental asthma. Interestingly, bispecific antibody fragments that cross-linked CD300a with Kit or with CCR3 abrogated mast cell–dependent inflammatory processes, in vitro and in vivo.

Conclusion

Present throughout the body, mast cells are involved in a variety of processes. Although mast cell–dependent pathogenic processes are better known, mast cell–dependent protective processes are increasingly recognized. Noticeably, mast cells are among the few cells whose activation can lead to death within minutes. Under physiological conditions, however, mast cell activation remains unapparent. All things considered, it therefore makes sense that mast cell activation be tightly controlled. The many receptors expressed by mast cells that trigger positive and negative signals can account for this control. As a consequence, either a failure of receptors to fulfill their task or an excess of their activity may affect the balance that keeps mast cell activation within the limits of physiology. A better knowledge of mast cell receptors and of their functioning is essential to unravel the etiology of inflammatory diseases such as allergy and to devise new therapeutic tools that will hopefully treat causes rather than symptoms.

Cross-References

- ▶ IgE Receptor
- ▶ Leukotriene Modifiers
- ▶ mAbs (omalizumab)

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▶ Mast Cells, Growth and Development
▶ Mast Cell Mediators
▶ Mastocytosis
▶ Role of IgE in Disease
▶ Role of Mast Cells in Diseases
▶ Specific IgE

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Allergen Avoidance: Avoidance Strategies for Skin Allergies

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Synonyms

Delayed skin reaction; Eczema; Hives; Irritant reaction

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Definition

The term skin allergies can refer to a multitude of different dermatologic conditions of varying pathophysiology. These include allergic conditions caused by immediate hypersensitivity IgE-mediated, delayed type 4 hypersensitivity, combination IgE and cell-mediated, and irritant reactions. Some examples include atopic dermatitis, dermatitis herpetiformis, allergic contact dermatitis, irritant contact dermatitis, latex allergy, and urticaria.

Atopic Dermatitis

Atopic dermatitis, also known as atopic eczema, is a skin disorder that usually presents in early childhood and is often the first part of the phenomenon known as the "atopic march" (subsequent development of asthma and allergic rhinitis). The skin may start as being erythematous and pruritic with edema and vesicular lesions that with scratching becomes lichenified and thickened in appearance. Atopic dermatitis is associated with the subsequent development of IgE sensitization to food and environmental allergens but is certainly not required. The skin barrier disruption in atopic dermatitis might provide a portal in which patients become sensitized to these allergens (Bieber 2008; Volcheck 2009).

Dermatitis Herpetiformis

Usually, dermatitis herpetiformis is associated with current celiac disease and manifests as a pruritic, red rash involving extensor areas including the knees and elbows as well as the scalp. The lesions can be varied with vesicles, papules, and hives (James and Burks 2009).

Allergic Contact Dermatitis

Allergic contact dermatitis (ACD) is a type IV cell-mediated reaction that is usually delayed and involves capture of allergens via dendritic cells at the skin with further presentation to T cells and inflammation. As this process involves antigen processing and presentation, the symptoms of erythema, pruritus, papulovesicular eruption, and skin thickening can occur hours to days after antigen exposure. Commonly implicated antigens include metals, cosmetics, adhesives, poison ivy/oak/sumac, fragrances, and even topical corticosteroids. Body areas that are commonly exposed to these substances include the face, eyelid, hands, and feet (Fonacier et al. 2010).

Irritant Contact Dermatitis

Irritant contact dermatitis (ICD) is mediated through a non-immunologic mechanism with inflammatory reaction. As the mechanism is different from ACD, the symptoms typically start sooner. ICD is usually limited to the areas of contact with the irritant substances and has sharp demarcation (Fonacier et al. 2010).

Latex Allergy

Natural rubber latex allergy can provoke both IgE-mediated symptoms, such as angioedema, urticaria, and anaphylaxis, as well as contact dermatitis. Diagnosis of latex-type 1/IgE-mediated allergy is made via clinical history symptoms with exposure as well as consideration of serum-specific testing IgE to latex and nonstandardized skin prick testing to latex extract made from gloves. Negative serum-specific testing and skin testing cannot entirely exclude latex allergy. Contact dermatitis due to latex is determined from clinical history as well as patch testing (Grammer 2009).

Urticaria

Urticaria, otherwise known as hives, is a pruritic and erythematous skin condition in which an individual lesion lasts less than 24 h. Acute urticaria is defined as less than 6 weeks duration as opposed to chronic urticaria which should be near daily lasting over 6 weeks. Acute urticaria can be

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caused by a viral infection, allergic IgE exposure such as food, medication, and less likely aeroallergen. Physical urticaria is caused by a physical stimulus such as pressure, vibration, cold, or heat exposure. Most chronic urticaria is "idiopathic" in nature (likely over 80 % of cases) as opposed to less than 5 % IgE mediated (Fonacier et al. 2010).

Avoidance Strategies: Atopic Dermatitis

True IgE-mediated food allergy is more prevalent in children with atopic dermatitis, but what role food-specific IgE plays in worsening of atopic dermatitis is unclear (James and Burks 2009). In certain patients, food ingestion is associated with worsening atopic dermatitis which occurs usually outside of the 2-h window seen with IgE-mediated food allergy. The most commonly associated foods include milk, wheat, egg, soy, and peanut. It is unclear what the mechanism of this association is but might be a combination of IgE mediated and cell mediated. Occasionally, a trial of elimination and retrial diet can be used for suspicious foods or observed food challenge with prolonged monitoring of skin for worsening atopic dermatitis. At this time, it is controversial whether or not skin testing or IgE food-specific testing is helpful for identifying such foods in patients who lack traditional IgE-mediated food allergy symptoms (Volcheck 2009; Greenhawt 2010).

In regard to environmental allergies such as dust mite sensitivity, dust mite avoidance measures with bedding encasement and frequent washing can help to minimize cutaneous exposure to dust mite allergens which have protease activity. Animal dander and pollens also may worsen atopic dermatitis, and avoidance measures discussed elsewhere could be implemented. Fragrance-free detergents are also less irritating to skin, and fabric softeners should be avoided. Irritative fabrics such as wool can also increase pruritus, as well as occlusive clothing. Perspiration that remains on the skin can also increase inflammation (Dai 2007; Volcheck 2009; Caubet and Eigenmann 2010). Patients with atopic dermatitis have increased rates of skin colonization with *Staphylococcus aureus* which leads to inflammation secondary to toxin production and possible toxin-specific IgE formation (Bieber 2008). Superinfection of the inflamed skin is also common. Treatment of the colonization and superinfection can involve topical and systemic antimicrobials. Recently, obesity has been shown to have an association with more severe atopic dermatitis (Sicherer and Leung 2012).

Treatment of atopic dermatitis is targeted at good skin care to improve the skin barrier function with moisturization including regular bathing and moisturizer application and minimization of inflammation through avoidance of triggers, topical corticosteroids, and treatment of cutaneous superinfection. Topical antihistamines should be avoided as there is an increased risk of contact sensitization with these products. Other treatments for atopic dermatitis include oral antihistamines for pruritus, wet dressing, topical calcineurin inhibitors, systemic corticosteroids, phototherapy, and immunosuppressants (Volcheck 2009; Sicherer and Leung 2011; Sicherer and Leung 2012). There is emerging evidence for improvement of atopic dermatitis symptoms with allergen immunotherapy to dust mite (Cox et al. 2011).

Avoidance Strategies: Dermatitis Herpetiformis

Gluten is the usual stimulus for the rash and improves upon elimination (James and Burks 2009).

Avoidance Strategies: Allergic Contact Dermatitis

Patch testing helps to identify the problematic compounds. Careful exposure and occupational history are needed to identify potential allergens for patch testing. Avoidance of clinically relevant compounds found to cause reactions on patch testing is necessary for long-term improvement of symptoms. Compliance with avoidance is

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improved if the provider is able to identify safer alternatives for the patient. In patients who cannot avoid contacting these substances, barrier methods such as gloves and covers might be an alternative (Fonacier et al. 2010).

Though the incidence of ACD is lower in children in early life, this rate increases to near adult levels by 10 years of age. Substances such as nickel can cause ACD in children and might be precipitated by early ear piercing. Suggested avoidance tactics for ACD prevention in children include fragrance- and preservative-free topical products, delayed ear piercing above 10 years of age, and judicious use of topical corticosteroids (Kütting et al. 2004). Also in countries whose laws regulate the amount of nickel content and release from products that touch the skin, there have been decreasing rates of nickel contact sensitization (Prakash and Davis 2010).

Avoidance Strategies: Irritant Contact Dermatitis

A careful history can help elucidate the problematic substance which then should be avoided (Fonacier et al. 2010). Activities such as exposure of skin to liquid greater than 2 h a day, use of occlusive gloves, or frequent hand washing are common causes of ICD. Physical conditions such as cold exposure, heat/sweating with occlusion, and friction can all cause or exacerbate ICD. Frequent use of moisturizer can improve symptoms (Slodownick et al. 2008).

Avoidance Strategies: Latex Allergy

Patients with either sensitivity should avoid these products, and patients with IgE latex allergy should have epinephrine auto-injector available and consider wearing a MedicAlert bracelet. Certain foods have cross-reactivity to latex such as bananas, kiwi, chestnuts, and avocado, and patients should be counseled regarding this (Grammer 2009). Non-latex medical products should also be used for latex-sensitive individuals such as nitrile gloves or silicone urinary catheters.

Avoidance Strategies: Urticaria

A thorough patient history and review of systems is needed to identify acute versus chronic urticaria, allergenic triggers, and physical urticaria triggers. Confirmation of physical urticaria can be made with challenge testing such as ice cube, pressure application, vibratory vortex exposure, exercise, and passive heat exposure. If an allergenic or physical trigger can be identified, usually in the context of acute urticaria, this should be avoided.

Cross-References

- ▶ 3-Dimethylaminopropylamine (DMAPA), Allergic Contact Dermatitis to
- ▶ Allergen Immunotherapy, Overview
- ▶ Allergic Contact Dermatitis
- ▶ Allergic Contact Dermatitis from Exotic Woods
- ▶ Atopic Dermatitis
- ▶ Contact Allergy to Hair Dyes
- ▶ Contact Allergy to Shoe Components
- ▶ Contact Dermatitis Due to Topical Drugs
- ▶ Contact Urticaria and Protein Contact Dermatitis (to Asparagus, Cow's Hair, Seafood, Etc.)
- ▶ Dermatitis from 2-*N*-Octyl-4-Isothiazolin-3-One, Allergic Contact
- ▶ Emergent Allergies in Cosmetics
- ▶ Eyes and Eyelid, Contact Allergic Reaction On
- ▶ Fingernails from Sensitization to Acrylic, Loss of
- ▶ Fragrancy, Allergic Contact Dermatitis
- ▶ Gluten Intolerance and Skin Diseases
- ▶ Hairdressers' Occupational Skin Disease
- ▶ Immunomodulator Therapy of Chronic Urticaria
- ▶ Methyldibromo Glutaronitrile, Contact Allergy to
- ▶ Nail Contact Dermatitis, Including Allergic Contact Dermatitis Due to Nail Cosmetics
- ▶ Nickel Allergic Contact Dermatitis
- ▶ Occupational Contact Dermatitis Due to Acrylates and Methacrylates
- ▶ Photoallergic Contact Dermatitis
- ▶ Plants, Allergic Contact Dermatitis from

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- ▶ Polidocanol: A Contact Allergen in Shampoo
- ▶ Sensitization and Allergy to Natural Rubber Latex
- ▶ Titanium Alloy, Dermatitis, Allergic Contact, Granulomatous
- ▶ Topical Antihistamines
- ▶ Topical Corticosteroids
- ▶ Topical Preparations: Calcineurin Inhibitors
- ▶ Urticaria

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Allergen Avoidance: Cockroach and Rodent Avoidance

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Synonyms

Insect allergy; Mouse allergy; Rat allergy

Definition

Cockroaches inhabit home environments, particularly in urban areas, and can be a significant contributor to allergic disease via IgE sensitization (Wallace et al. 2008). Up to 40 % of patients with asthma in urban areas have cockroach sensitization compared to 20 % in suburban areas where there are fewer people living in a given area with fewer food particles and water sources (Volcheck 2009; Peden and Reed 2010). There are thousands of species of cockroach, but only five are commonly found in homes: German (*Blattella germanica*), Oriental (*Blatta orientalis*), American (*Periplaneta americana*), smoky brown (*Periplaneta fuliginosa*), and brown banded (*Supella longipalpa*). The German cockroach is the main contributor to cockroach allergy in North America, but the American cockroach is important as well. The German cockroach is brown in color and about 16 mm long, while the American cockroach is 38 mm in length with brown wings (Eggleston and Arruda 2001).

Mice and rats are the more common rodents that are associated with human allergic disease. Exposure to these animals can happen in the home environment, as unwanted inhabitants especially in inner city or as pets, as well as in the work environment such as laboratories that use these animals. In laboratory workers, symptoms of sensitization usually develop within 2–3 years of exposure. In some inner-city areas, up to 25 % of children have demonstrable IgE

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sensitivity to mouse (Bush 2008; Brooks and Bush 2009; Volcheck 2009).

Cockroach Allergen

The cockroach allergen particles are larger than 10 μm and settle quickly after environmental disturbance. Studies have shown that a level of cockroach exposure of 2 units (U) of Bla g 1 per 1 g of dust is the likely threshold for allergic sensitization in susceptible individuals and 8 U/g for development of asthma symptoms. The major allergens of the German cockroach are Bla g 1 and Bla g 2 which are found in frass (cockroach excretory matter) and the body. This includes saliva, dead bodies, and shed skin. Allergens of the American cockroach include Per a 1, Per a 3, and Per a 7. Bla g 1 and Per a 1 are cross-reactive, and the remainder is largely species specific. Bla g 1 and Per a 1 show sequence homology to a mosquito protein that may have digestive function. Bla g 2 is similar in sequence to aspartic proteases and is found in the cockroach digestive tract. Bla g 2 can increase if the cockroach ingests boric acid at nonlethal doses. Per a 3 is a storage protein, and Per a 7 is similar in sequence to tropomyosin which is found in mites and shrimp (Eggleston and Arruda 2001; Eggleston 2005; Bush 2008; Brooks and Bush 2009; Volcheck 2009).

Cockroach Avoidance

Cockroaches favor dark, humid, and warm areas to inhabit with adequate access to food and water sources. They tend to also settle in small areas such as cracks in walls or floors. They generally stay in these areas except at night when they emerge to feed. Some inhabitants might not be aware of hidden cockroach infestation; therefore, it is necessary to carefully examine areas around the home, particularly in the kitchen, for signs of cockroach and possible placement of sticky traps to identify their presence. If cockroaches are seen during daytime, it is usually a sign of large infestation. If cockroaches are identified, then changes should be made to rid the home of them including cleaning any exposed food or garbage, washing of dishes promptly, and properly closing trash cans. Consideration of sealing visible cracks may be made. Odorless gel insecticide and bait can be placed to remove living cockroaches. Commonly used insecticides include boric acid, hydramethylnon, abamectin, and fipronil. In some cases, professional extermination services should be used in extensive infestations. Integrated pest management is recommended and involves the use of insecticides in select areas to minimize exposure to humans and pets. After the infestation is controlled, thorough cleaning should be performed to remove feces and any dead cockroaches. This includes frequent vacuuming, washing of surfaces with detergent or dilute bleach solution to remove allergen, and washing of all bedding and washable fabrics. It is unclear if interventions such as high-efficiency particulate air (HEPA) filters or encasement of mattresses and pillows are effective. It can take up to 6 months of cleaning measures for the majority of cockroach allergen to be removed from the environment even after elimination of the infestation. In addition, proper maintenance after infestation is important to keep allergen levels low (Eggleston and Arruda 2001; Custovic et al. 2002; Eggleston 2005; Bush 2008; Wallace et al. 2008; Grammer and Harris 2009; Platts-Mills 2009; Volcheck 2009; Bush 2011).

Rodent Allergen

Mus m 1 is the major mouse allergen and the main allergen in mouse urine. The allergenic particles are usually 0.05–10 μm and therefore likely to remain airborne for longer periods of time (Eggleston 2005; Volcheck 2009). As well, these particles have been shown in the laboratory setting of being able to be carried to mouse-free rooms remote from the area that houses the mice (Wood 2001).

Rat n 1 is the major rat allergen that is found in the urine and is carried on particles less than 7 μm in size but can range from 1 to 20 μm (Wood 2001; Brooks and Bush 2009; Volcheck 2009).

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Rodent Allergen Avoidance

In the home environment, if there is an infestation of rodents (more likely to be mice), this should be managed with integrated pest management. Integrated pest management includes targeted pesticides, sealing of access points from the outdoors, elimination of food and water sources, and thorough cleaning of areas where rodents were found (Eggleston 2005; Tovey 2008). Integrated pest management strategies have shown to decrease mouse allergen Mus m 1 over a 5-month period as compared to control homes though no difference in FEV_1 or asthma symptoms was noted with this intervention (Phipatanakul et al. 2004).

The prevalence of laboratory animal allergy in workers is approximately 20 % with the majority being sensitized to mouse and rat. The likelihood of sensitization increases with direct exposure and handling of the rodent (Wood 2001). In the work environment, the highest exposure to mouse and rat allergen usually occurs with cleaning and emptying of cages and feeding the animals (Wood 2001; Volcheck 2009). Reducing animal allergen exposure is achievable with engineering controls, procedural, and personal protective equipment (Harrison 2001; Gordon and Preece 2003). Buildings should be adequately designed for proper ventilation and air exchange. To lessen exposure in laboratory workers, cages with individual ventilation produce less environmental rodent allergen as well as negative pressure. These cage systems when run with negative pressure have reduced ambient rodent allergen by greater than 75 % (Wood 2001). Robotic cage handling and washing reduce worker exposure as well but require costly equipment. Using absorbent padding in the cages reduces allergen exposure as well (Wood 2001). Workers can also use individual motorized filtration and ventilation units or other types of personal respirators (Brooks and Bush 2009; Volcheck 2009). In an interventional study involving work-practice modification (reducing animal density), engineering controls (filter-top cages, HEPA room ventilation, increased air exchange, dust-free bedding), and personal protective equipment (respirator), one group was able to substantially reduce incidence of laboratory animal allergy (Fisher et al. 1998).

Cross-References

- ▶ Analytes and Biomarkers: Environmental Allergen Assessment
- ▶ Asthma Variants: Allergic Asthma
- ▶ Role of IgE in Disease

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Allergen Avoidance: Dietary Management of Food Allergy

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Synonyms

IgE-mediated food allergy; Non-IgE-mediated food allergy

Definition

Commonly the term food allergy is used to mean an immediate IgE-mediated reaction to food, but a variety of other immune-mediated reactions to food also exist. Other food allergy includes food protein-induced enterocolitis, eosinophilic gastroenteritis and esophagitis, and worsening of atopic dermatitis.

IgE-Mediated Food Allergy

IgE-mediated food allergy is characterized by an acute onset of symptoms triggered by an IgE food-specific antibody interacting with mast cells and basophils upon ingestion of the food. Symptoms usually start within 2 h of consuming the food secondary to histamine release and synthesis of other mast cell mediators such as leukotrienes. Symptoms include cutaneous flushing, urticaria/hives, angioedema, bronchospasm, vomiting, diarrhea, and hypotension and can occur in any combination. Anaphylaxis can occur and can be fatal. Identification of suspected IgE-mediated food allergy is made when a clinical event consistent with IgE-mediated food allergy is correlated with a food-specific positive IgE serum or skin test. In general, screening for food allergy is not recommended without a clinical history for a suspected food as people can have positive IgE testing in the serum or skin despite lack of clinical allergy and are able to tolerate the food. This phenomenon is termed sensitization. People with other atopic disease, particularly atopic dermatitis, have a higher likelihood of having positive tests to food with lack of clinical allergy. The most specific manner to diagnose food allergy is a double-blind placebo-controlled food challenge, though this is not often done in clinical practice and single-blind or open challenge might be more feasible (Boyce et al. 2010; Sicherer and Sampson 2010; Burks et al. 2012).

Once a food allergy is identified, the patient should avoid the food and be instructed on the proper use of epinephrine auto-injector in the event of accidental exposure. Reviewing the proper use of epinephrine auto-injector is important as well as verifying the correct dose, knowledge about proper storage, and expiration date. Epinephrine is the preferred treatment for food-induced IgE symptoms. If epinephrine auto-injector is used, the patient should seek emergency care to monitor for recurrence of symptoms (biphasic reaction that occurs in 20 % of cases) (James and Burks 2009).

Certain IgE-specific food allergies in young children remit such as cow's milk, soy, wheat, and egg often later in life. Other allergens, such as peanut, tree nut, fish, and shellfish, are less likely to be outgrown. Foods that have high cross-reactivity should be avoided. For example, if a patient has an allergy to a particular tree nut, then generally other tree nuts should be avoided as a group as well. Severity of the reaction can

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depend on the quantity ingested and the manner it was prepared. In particular cases, patients are able to tolerate foods in cooked forms but not in uncooked form. Unfortunately, no clinical tests exist to date to predict which patients would be able to tolerate a baked product, and an observed food challenge is needed to determine this (Boyce et al. 2010; Burks et al. 2012).

A variety of strategies are clinically used to determine if a person continues to have sustained food allergy after a period of time of food avoidance. One strategy is to require skin and blood IgE testing to the food to be negative before performing an oral food challenge. If the patient passes the oral challenge without symptoms of IgE-mediated allergy, then likely they would tolerate the food in the future with continued exposure. Another strategy is to try to challenge patients with declining levels of food-specific IgE antibody. As people can tolerate food despite positive blood tests, there are some people who might be able to tolerate a food challenge once a trend for decreasing IgE is seen. There have been 95 % positive predictive value and specificity thresholds published based on IgE serum food-specific antibody levels that predict possible tolerance of a food with a history of food-specific allergy. Some clinicians will offer patients a food challenge once IgE serum testing reaches below those levels. Importantly, food challenge testing should be done in a facility capable of managing anaphylaxis as severe reactions can occur despite negative testing as well. Once a food challenge is passed, the food that was previously avoided should be consumed on a regular basis to maintain oral tolerance (James and Burks 2009; Boyce et al. 2010; Sicherer and Sampson 2010; Burks et al. 2012).

Strict food avoidance is generally recommended if a food allergy is identified. The patient and family should be properly educated on tools available to avoid problematic foods. Careful reading of labels is recommended, and particular attention paid to inquiring at restaurants about ingredients prior to consuming foods. High-risk areas for food consumption include buffets, ice cream shops, and cuisines with high use of patient-specific food allergy such as fish/shellfish/nuts. In the home, it is important to avoid cross-contamination. Certain foods such as peanut and tree nut can be more easily removed from the entire household, while milk, egg, and wheat are more universal in diets. In the case where the food is not removed from the house, it might be safer for the patient to have designated containers or utensils used to prepare, store, and consume food. Food labeling in the United States is regulated by the government, and recent laws require manufacturers to label peanut, tree nuts, fish, shellfish, wheat, egg, milk, and soy ingredients in plain words. This labeling helps patients and families to interpret often confusing food labels. Labels often contain the advisory terms that a food was processed in an area where another allergenic food might have been. The levels of cross-contamination when studied have been highly variable, and the usual recommendation is to avoid the food with these labels. In children with multiple food allergies, working with a nutritionist is helpful to ensure adequate nutrition for growth and development (James and Burks 2009; Sicherer and Sampson 2010; Kim and Sicherer 2011).

There are also certain people who develop food-dependent, exercise-induced anaphylaxis. This is most commonly seen with wheat, shellfish, and celery and is associated with anaphylaxis symptoms after ingestion of the food followed by exercise. Some patients have symptoms as well with any food eaten before exercise. A few cases of ingestion postexercise have also been associated with symptoms. These patients should avoid eating these foods at least 4–6 h prior to exercise and ideally have epinephrine available during exercise if symptoms were to develop and to not perform exercise alone (James and Burks 2009; Burks et al. 2012).

Non-IgE-Mediated Food Allergy

These conditions are generally thought to be cell mediated or possibly combined IgE and cell mediated. It is unclear if IgE sensitization

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predicts a problematic food in conditions such as eosinophilic esophagitis or gastroenteritis. Strategies that have been employed for dietary management of the eosinophilic gastrointestinal diseases include elimination and retrial diets. A variety of ways to identify which foods to eliminate have been proposed: based on skin/blood IgE testing, food patch testing, elemental diet, and elimination of more commonly implicated foods. There is no standardized test though to identify the implicated food. Usually this is combined with medical management such as topical and systemic corticosteroids and proton-pump inhibitors. Once a food is avoided, clinicians can monitor for improvement of symptoms and take biopsy samples to prove improvement in eosinophil counts and worsening of symptoms upon reintroduction. Generally the food in question should be avoided for 4–6 weeks prior to decision made regarding the benefits and decision on further restriction versus attempt at reintroduction (Burks et al. 2012).

Food protein-induced enterocolitis (FPIES) usually affects infants and results in vomiting, diarrhea, and poor growth. Patients can have severe symptoms after a challenge such as dehydration secondary to vomiting and diarrhea and hypotension usually within 2–3 h of eating the food. The most commonly implicated foods are cow's milk, soy, and rice. Generally these foods can be reintroduced after 3 years of age (James and Burks 2009; Burks et al. 2012).

Food-induced colitis or proctocolitis refers to blood-streaked stool or loose stools associated with breastfeeding, soy, or milk formula. The patients are usually clinically well unlike FPIES, and elimination of the food usually resolves symptoms. Casein hydrolysate formula or even elemental formula can be used, and symptoms usually resolve by 1 year of age (James and Burks 2009).

Pollen-Food Allergy Syndrome

Pollen-food allergy syndrome, or oral allergy syndrome, results from a cross-reactivity of a pollen specific IgE and the fragile allergens in certain raw fruits and vegetables. Some of these fragile allergens are termed profilins. Generally the symptoms are isolated to the mouth and consist of itching and mild edema. There is a low incidence of anaphylaxis (<1–2 %). People with this condition are able to tolerate these foods in cooked format without symptoms and should avoid the raw food. Common relationships include birch allergy and symptoms with raw apple, peach, pear, and ragweed with melons. These symptoms may be more prominent during the associated pollen season (James and Burks 2009; Volcheck 2009; Burks et al. 2012). Some clinicians chose to give patients with this syndrome epinephrine auto-injector for the low likelihood of anaphylaxis.

Prevention of Food Allergy

To date, there are no clear-cut guidelines on how to prevent food allergy among children. Previous American Academy of Pediatrics recommendations included avoidance of particular foods, milk, egg, and peanut/tree nut in early infancy. Current American Academy of Pediatrics (AAP) recommendations have changed to advise that there is no evidence to support delayed introduction of solid foods beyond 4–6 months of age. There are some indications that delayed introduction of foods might increase food allergy possibly via cutaneous sensitization to food in the environment rather than gaining oral tolerance if the food were fed. There is conflicting evidence of whether or not maternal avoidance of foods such as peanut during gestation or breastfeeding is helpful or not (Sicherer and Leung 2011; Lack 2012; Sicherer and Leung 2012).

Future

Currently, the only approved dietary approach to food allergy is avoidance until clinical tolerance is demonstrated. Currently, research-based trials of oral immunotherapy and sublingual immunotherapy are underway. In addition, active

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feeding of baked milk or egg products may help promote whole milk tolerance in milk- and egg-allergic children. Other techniques such as epicutaneous immunotherapy with traditional and modified allergens, manufactured peptides, Chinese herbal formulas, and anti-IgE monoclonal antibodies are also being studied as therapeutic options (Nowak-Węgrzyn and Sampson 2011; Sicherer and Leung 2011; Burks et al. 2012; Sicherer and Leung 2012).

Cross-References

- Allergic Proctocolitis and Food Protein-Induced Enterocolitis Syndrome (FPIES)
- Analytes and Biomarkers: IgE
- Cow's Milk Allergy
- Delayed Anaphylaxis to Mammalian Meat (Alpha-Gal)
- Diagnostic Food Challenges
- Egg Allergy
- Eosinophilic Esophagitis
- Eosinophilic Gastrointestinal Disorders
- Epidemiology of Food Allergy
- Fatal Allergic Reactions to Foods
- Food Allergens
- Food Allergies, Diagnostic Testing
- Food Allergy and its Future Treatment
- Food Allergy, Overview
- Food Desensitization
- Nutrition in Food Allergy
- Oral Allergy Syndrome
- Peanut Allergy
- Role of IgE in Disease
- Specific IgE

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Allergen Avoidance: Dust Mite Avoidance

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Synonyms

Environmental allergens; House dust allergy; Indoor allergens; Mite allergy

Definition

House dust mite exposure is associated with allergic asthma, perennial rhinitis, and atopic dermatitis. Dust mites are about 0.33-mm-long arachnids with eight legs (Brooks and Bush 2009). In temperate climates, the most common species of dust mites associated with allergic sensitization in the United States are *Dermatophagoides farinae* and Dermatophagoides pteronyssinus. Euroglyphus maynei may be found in other temperate

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climates while in the tropics and in the subtropics Blomia tropicalis predominates (Arlian and Platts-Mills 2001).

Allergen Structure

Dust mite allergens are broken down into multiple groups, 1–13. In groups 1 and 2, allergens are approximately 25 and 14 kDa in molecular weight, respectively. Group 1 allergens are glycoproteins which have cysteine protease activity which may have a role in development of atopic sensitization (Arlian and Platts-Mills 2001). The major allergen for *Dermatophagoides pteronyssinus* is Der p 1. The other major dust mite allergen in North America is Der f 1, for *Dermatophagoides farinae*, also a cysteine protease. There is greater than 80 % of homology between Der p 1 and Der f 1, but patients can show sensitization to one or the other exclusively. Dust might allergens are found in the fecal material of the mites and in the body, though major allergens are found mostly in the fecal matter (Brooks and Bush 2009).

Group 2 allergens are Der f 2 and Der p 2 which show >80 % sequence homology and may originate from the male reproductive tract (Arlian and Platts-Mills 2001).

Habitat

Dust mites primarily feed off sloughed human epithelial cells and are dependent on relative humidity for water. Mites proliferate when relative humidity is greater than 60 % and are temperature dependent at 40–50 % relative humidity, but larval forms can survive lower humidity conditions (Brooks and Bush 2009). The ideal temperature to support greatest population growth of *D. pteronyssinus* is about 25 °C. In North America, most homes contain both *D. farinae* and *D. pteronyssinus*, but usually one species predominates. This predominance does not appear to be geographically limited (Arlian and Platts-Mills 2001). There does appear to be a seasonal variation in house dust mite concentration where mite growth is highest during summertime with high indoor relative humidity (Volcheck 2009).

The mite allergen particles generally average 20 μm, therefore settle quickly from any disturbed air (Arlian and Platts-Mills 2001). Very little (<1 ng/ml) dust mite allergen is detected in undisturbed conditions (Platts-Mills 2009). Dust mites are in highest concentration in mattress dust but are present in all fabric upholstery, furniture, and carpeting (Brooks and Bush 2009). In addition, dust mites can be found in lower quantities on non-fabric environments such as leather furniture and hard floors (Volcheck 2009).

Avoidance Measures

Unfortunately, no single avoidance measure will be effective in controlling dust mite exposure or producing clinical change in symptoms secondary to mite exposure (Nurmatov et al. 2012; Wallace et al. 2008). There is evidence that with sustained decreased dust mite allergen exposure, there are improvements in asthma and atopic dermatitis symptoms. Yet achieving sustained decreases is difficult as it can take long periods of time and usually involves multiple measures (Platts-Mills 2009). A recent meta-analysis suggested possible reduction in rhinitis symptoms with combined measures of acaricides and bedroom interventions (Nurmatov et al. 2012). Studies to prove efficacy of interventions have been few. A variety of proposed mechanisms to avoid house dust mites include encasement of bedding, hot washing of bedding, removal of carpet, use of acaricides and tannic acid on carpets and furniture, minimization of upholstered furniture, HEPA-filtered vacuuming, and reduction of humidity (Bush 2008).

Dust mite avoidance measures have generally been targeted at bedtime exposures as 50–60 % of mite exposure happens in bed (Tovey 2008). House dust mite allergen particles generally do not remain airborne long after disturbance of house dust as the particle size is relatively large (10–30 μm). Allergen-proof encasings are often recommended to patients that are impermeable to

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mite allergens with pore size less than 10 μm (Arlian and Platts-Mills 2001). These encasements should be used on mattress, box springs, pillows, and to cover any comforters or duvets. The degree to which dust mite allergen can be reduced with encasement of bedding is not universally established, but studies seem to show that the allergen level does not increase (Eggleston 2005).

Other bedroom exposure avoidance methods include targeting removing dust mite allergen, and killing of ova includes hot washing and drying of all bed clothing over the impermeable covers with detergents to temperature greater than 130 °F at least every 2 weeks. Removal of carpeting will also eliminate another reservoir for mites, especially in areas where carpet is installed over concrete (Wallace et al. 2008). Freezing of soft-toys for 24 h that cannot be washed is another method of killing allergen (to −17° to −20 °C); although, washing would be needed to remove the mite allergen (Arlian and Platts-Mills 2001). Dry cleaning of non-washable fabrics does kill mites but also does not necessarily remove the allergen. Substitution of blinds for drapes and vinyl or leather upholstery could also be considered (Volcheck 2009).

Reduction in relative humidity in living environments would also be thought to help control dust mite proliferation as they are dependent on ambient humidity for water. This has been difficult to practically achieve in climates where dust mites thrive. Recommendations include reducing relative humidity to less than 50 % via air-conditioning or a dehumidifier (Wallace et al. 2008).

Use of acaricides (benzyl benzoate) or 3 % tannic acid can be used to kill and denature mite allergen, respectively, and has shown efficacy in some laboratory studies and small trials (Tovey 2008; Nurmatov et al. 2012) These agents temporarily reduce mite allergens but need to be repeated as frequently as every 6 weeks (Platts-Mills 2009).

Weekly vacuuming is also generally recommended but does not remove significant amount of allergen as areas close to the base of the carpet are not usually accessed. There might be a benefit to have the sensitized patient either avoid performing the vacuuming or to wear a mask while vacuuming and to allow time for disturbed mite particles to resettle before reentering the room. High-efficiency particulate air (HEPA) filtration on vacuums or central-vacuuming are also options but have not shown to be universally effective in reducing allergen exposure. In addition, air filtration systems and duct cleaning are not thought to be especially effective as dust mite particles tend to settle quickly from the air dust to their size (Arlian and Platts-Mills 2001; Tovey 2008; Grammer and Harris 2009). Steam cleaning of fabrics and carpets can remove surface population of mites but does not remove the mites at the base; in addition, residual moisture may further increase mite growth (Volcheck 2009).

Cross-References

- ▶ Analytes and Biomarkers: Environmental Allergen Assessment
- ▶ Asthma Variants: Allergic Asthma
- ▶ Role of IgE in Disease

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Allergen Avoidance: Fungi and Mold Avoidance

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Synonyms

Environmental allergens; Indoor allergens; Outdoor allergens

Definition

Fungi, often referred to as mold, can be both indoor and outdoor allergens. The allergenic portions are the mycelia (filamentous hyphae) and spores. Though there are large amounts of fungi that are available for testing for allergic sensitivity and present in the environment (>100), only a few have demonstrated clear association with atopic disease (*Alternaria, Aspergillus, Cladosporium, Penicillium*). Fungal allergen levels can be quite high and present both seasonally and perennially. In the United States, northern areas tend to see higher levels of fungal allergen in late spring and late summer as opposed to southern areas where levels can be elevated throughout the year (Wallace et al. 2008). Fungal allergic burden is difficult to assess as spores are used to identify them from culture and allergenic fragments are not counted which likely leads to underestimation (Brooks and Bush 2009; Shah and Grammer 2012). Fungi can produce both sexual and asexual spores, and classification is based on the characteristics of the spore. The major classes of allergenic fungi include the zygomycetes, basidiomycetes, and ascomycetes (some classify the deuteromycetes as part of the ascomycetes versus a separate class entirely) (Volcheck 2009).

Classification

Zygomycetes produce spores that are found in damp areas such as basements and compost and include the allergenic species *Rhizopus nigricans* and *Mucor racemosus*. Basidiomycetes include the Homobasidiomycetidae (mushrooms, bracket fungi, and puff balls which are found to be higher during the night and environmental humidity) and the Heterobasidiomycetidae (rusts, smuts, jelly fungi which can be found on cereal grains and agricultural environments). Ascomycetes produce spores in sacs and produce large amount of spores especially in high humidity. *Saccharomyces cerevisiae* (baker's yeast) is a member of this class. Deuteromycetes make asexual spores called conidia. These include *Aspergillus, Penicillium, Alternaria, Cladosporium, Helminthosporium, Fusarium, Epicoccum, Curvularia, Drechslera*, and *Aureobasidium* (Brooks and Bush 2009).

Characteristics

Alternaria and *Cladosporium* are the most prevalent outdoor fungi in most areas and are present from spring to the first frost and need higher substrate moisture content. They are also known as "field fungi," as they are found in the soil. *Helminthosporium* and *Fusarium* are field fungi as well. This is opposed to the "storage fungi," including *Aspergillus* and *Penicillium* which do better with lower moisture content and are commonly found indoors. The classification of outdoor versus indoor can be misleading as traditionally "outdoor molds" can be found indoors as well during warm temperatures. Humidity usually supports most fungal growth though often drier conditions are needed along with wind to release spores (Brooks and Bush 2009).

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Alternaria is an important fungal allergen especially in asthma. The spores are about 20–60 μm. *Alternaria* is found year round with peaks from late summer to fall, especially in warm humid climates. Though it grows best in the field and among rotting plants and wood, it is commonly found inside homes. The major allergic component of *Alternaria alternata* is Alt a 1, with a high proportion of *Alternaria*-sensitive individuals showing IgE production. Alternaria exposure in sensitized individuals with asthma has been associated with respiratory arrest. *Cladosporium* is also an abundant fungal allergen especially in cooler climates during spring through fall. The major allergens are Cla h 1, Cla h 2, and Cla h 4. Aspergillus is the major trigger of ABPA (allergic bronchopulmonary aspergillosis) in which patients develop IgE and IgG antibodies to the fungus. There are a variety of species including *fumigatus*, *niger*, and *versicolor*. Aspergillus is usually found in homes, and the major allergen of *Aspergillus fumigatus* is Asp f 1. *Penicillium* is also found indoors (green mildew particularly in basements) with spores that are 2–4 μm (Brooks and Bush 2009; Volcheck 2009; Shah and Grammer 2012).

Fungal Avoidance

Most indoor fungal allergens are found in areas of higher humidity. In studies of fungal growth in homes, anywhere from 5 to over 40 species of fungi have been found (Tovey 2008). Ventilation of areas in the home with higher humidity, such as the kitchen and bathrooms, is important as well as keeping relative humidity below 50 %. Dehumidifiers in the basements are generally recommended as well as using air-conditioning during summer months. Areas that are subject to condensation (such as pipes) should be insulated from the rest of the home environment. Heating, ventilation, and air-conditioning (HVAC) systems should be properly maintained to avoid fungal growth within them and further dispersion through the home with circulation of air. Room filters, particularly HEPA (high-efficiency particulate air) filters, have some efficacy in reducing fungal allergen exposure but can be prohibitively expensive to install house-wide. Consideration of individual room air filtration units may be more reasonable. HEPA filters are generally thought to be more efficacious than electrostatic, ionic, or electronic air cleaners. Wall panels and wallpaper should be monitored for signs of fungal growth and either removed or treated with a bleach and detergent solution to remove the contaminated areas. Treatment of areas with fungicide or bleach solutions can reduce fungal growth but is best used in areas that are nonporous as fungi can penetrate beyond the reach of such solutions. Areas prone to flooding should be evaluated for interventions to reduce chances of water damage, and carpet and upholstered items should be avoided in these areas. Areas that have been subject to water damage should be thoroughly cleaned as soon as possible and ideally replaced (carpet with hard flooring). Carpet should be vacuumed regularly as well as ideally with a HEPA-filter-equipped vacuum (Bush and Portnoy 2001; Custovic et al. 2002; Bush 2008; Wallace et al. 2008; Grammer and Harris 2009; Volcheck 2009).

Outdoor fungal exposure can occur year round, but in cases such as Alternaria are found to be highest during particular seasons (late summer through fall). Therefore, outdoor activity during this time could be minimized in *Alternaria*-sensitive individuals. In addition, mold-sensitized individuals should avoid areas predisposed to fungal growth such as barns, compost piles, hay piles, and areas undergoing disruption of soil. Doors and windows should also be kept closed during high outdoor fungal seasons. Certain weather conditions, in particular thunderstorms, can be associated with significant elevations in fungal spore release. Vegetation around homes should be kept minimal, and prompt removal of leaf and plant debris should be performed before aggressive fungal growth can set in (Bush and Portnoy 2001; Custovic et al. 2002; Bush 2008; Wallace et al. 2008; Grammer and Harris 2009; Volcheck 2009).

Patients who have to be exposed to areas contaminated with fungus could also consider wearing a particulate mask if the area cannot be avoided (Bush and Portnoy 2001).

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Cross-References

- ▶ Analytes and Biomarkers: Environmental Allergen Assessment
- ▶ Asthma Variants: Allergic Asthma
- ▶ Role of IgE in Disease

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Allergen Avoidance: Furry Animal Avoidance

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Synonyms

Cat allergy; Dog allergy; Pet allergy

Definition

The most important furry animal exposures for allergy are the domestic cat and dog. Other furry animals that could be encountered in the home environment that are associated with allergenic sensitization include hamsters, guinea pigs, gerbils, mice, and rats. Occupational exposure can also happen in workers of laboratory facilities, farming (cattle), and recreational activity (horses) (Volcheck 2009). In the United States, approximately 60 % of households have at least one pet, the majority of which are cats and dogs (Reisacher 2011). Studies have shown that areas void of direct animal exposure, such as schools, daycares, and even homes, can have detectable cat and dog allergen due to its "sticky" nature (Eggleston 2005; Bush 2011). Despite claims by some companies of producing "allergy-free" pets, these animals do not exist as in both cats and dogs the allergenic components come from a variety of different basic animal structural proteins (Portnoy et al. 2012). Pet allergen is most concentrated in carpets though upholstered furniture and bedding can also have high concentrations. Levels of cat and dog allergen found in dust in homes can vary from 1 to 3,000 μg/g of dust with airborne levels of 10–200 ng/m^3 in homes with these animals (Chapman and Wood 2001).

Cat Allergen

Cat allergen particles range from 1 to greater than 20 μm and are very buoyant. The majority of particles will settle from disturbed air in 2 days, but the remainder may remain airborne for greater than 2 weeks. The amount of airborne cat allergen increases with the number of cats in the environment and goes up within 30 min of cat entrance to an area (Portnoy et al. 2012).

The major cat allergen is Fel d 1, secretoglobulin, which is found in over 90 % of cat-sensitized individuals. Male cats produce more Fel d 1 than females, but all cats produce clinically important levels. Fel d 1 is found on cat epithelia and hair follicles and is made in sebaceous, anal, and salivary glands. By grooming,

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cats transfer Fel d 1 from saliva onto fur (Bush 2011). Another ubiquitous allergen in cats is Fel d 2, cat albumin, and others such as Fel d 3 (cystatin, cysteine protease inhibitor), Fel d 4 (lipocalin), Fel d 5 (IgA), Fel d 6 (IgM), and Fel d 7 (lipocalin) (Custovic et al. 2002; Portnoy et al. 2012).

Cat Allergen Avoidance

The most effective way to reduce cat allergen exposure is to avoid cats. Even after removal of the cat, allergen levels may not reach levels comparable to homes without cats for up to 6 months. Thorough cleaning of the home with the below-listed techniques speeds this process (Chapman and Wood 2001; Eggleston 2005; Bush 2011). It is frequently difficult for pet owners to relocate their animals; therefore, a variety of allergen reduction techniques have been attempted. Allergen reduction methods may reduce amount of allergen concentration but often is not enough to make a considerable difference in symptomology or be clinically significant. Due to its buoyancy, cat allergen can be found on walls, and its concentration in dust can be quite different from airborne levels. Dust levels are higher in living rooms compared with other areas of the house. Homes with poor ventilation and higher humidity also tend to have higher concentrations of cat allergen if a cat resides there, and improved ventilation seems to help the dispersal of small particles (Portnoy et al. 2012).

As carpet is an important area for cat allergen accumulation, frequent vacuuming of these areas tends to reduce cat allergen in this area as well as replacing carpet with hard flooring. Because smaller cat allergen particles can remain airborne for up to 2 weeks, high-efficiency particulate air (HEPA) filters can reduce this time by removing the particles. Usually a multi-intervention approach is needed to reduce cat allergen levels including mattress and pillow encasements (woven microfiber, <6 μm pore size), removing the cat from the bedroom, vacuuming regularly with a central vacuum or high-efficiency vacuum, cleaning of hard surfaces with a sticky dust cloth, and HEPA filters in rooms, especially where the pet inhabits (Custovic et al. 2002; Wallace et al. 2008; Grammer and Harris 2009; Volcheck 2009; Reisacher 2011; Portnoy et al. 2012).

The clothing of people who own cats is likely the manner for allergen transference to areas where cat allergen can be found without direct cat exposure. People who do not own cats then likely acquire cat allergen on their clothing and transport it to their homes (Bush 2008; Portnoy et al. 2012).

Washing cats for 3 min weekly has shown to lead to a transient decrease in airborne allergen. Chemical treatments can be used to modify allergens already deposited in the home but do not lead to sustained decreased levels as long as the cat remains in the environment. Substances such as tannic acid can be used to denature allergens on carpets, upholstered furniture, etc., but repeat applications will be necessary. Hypochlorite bleach also reduces active allergen concentration but can be associated with respiratory symptoms, especially in patients with asthma. Washing of hands after handling cats or areas where the cat frequently lies upon might reduce inoculation into the eyes and respiratory tract (Reisacher 2011; Portnoy et al. 2012).

Dog Allergen

The major dog allergens include Can f 1 (lipocalin) mostly from the sebaceous glands, Can f 2 (lipocalin), Can f 3 (albumin), Can f 4 (odorant-binding protein), Can f 5 (arginine esterase), and Can f 6 (lipocalin). Close to 75 % of patients with dog allergy show sensitization to Can f 1 and Can f 2 (Chapman and Wood 2001). Again, due to the wide variety of dog allergens, there are no hypoallergenic dogs. Dog allergen particles are similar to cat allergen in terms of size where the majority are greater than 9 μm, but particles less than 5 μm are also present which remain airborne longer and contribute to lower respiratory symptoms. Unlike cats, the number of dogs does not affect the dog allergen concentration in the home, and levels are higher in rooms in which dogs are allowed. Dog allergen can also be

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found in about 15 % of homes without dogs. The carpet is the main area for dog allergen concentration, but like cat allergen, it can be found on smooth surfaces like walls (Portnoy et al. 2012).

Dog Allergen Avoidance

Recommendations for dog allergen avoidance are similar to those for cat allergen including removing the animal from the home and if not possible then excluding the animal from the bedroom, encasement of mattress/pillows, frequent vacuuming and cleaning of upholstered/hard surfaces, and HEPA filters. Washing the dog weekly can temporarily reduce levels of Fel d 1 in the air but is not sustained and will increase by the end of the week (Platts-Mills 2009; Volcheck 2009; Portnoy et al. 2012).

Cross-References

- ▶ Analytes and Biomarkers: Environmental Allergen Assessment
- ▶ Asthma Variants: Allergic Asthma
- ▶ Role of IgE in Disease

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Allergen Avoidance: Pollen Avoidance - Tree, Grass, and Weed

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Synonyms

Environmental allergens; Outdoor allergens

Definition

Pollen grains or particles are complex structures whose functions in plant reproduction are varied and play a role in allergenicity including enzymatic activity such as serine and cysteine proteases. Airborne pollens range in size from 20 to 60 μm which is thought to result in the majority of these allergens being presented to the upper respiratory system. Yet smaller pollen particles are found in the lower respiratory system and trigger asthma symptoms (Brooks and Bush 2009). Pollen grains are composed of the male reproductive portions of the plants. Allergenic portions of the grain are rapidly released from the grain upon contact with the mucosal surface (Wallace et al. 2008).

Wind-pollinated plants (anemophilous) have more significance in allergy as compared with insect pollinated (entomophilous) due to the

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greater concentrations found in the air and increased contact with respiratory mucosa. Pollen proteins play a wide variety of functions in plant biology such as roles in cell wall remodeling, profilins involved in actin polymerization, and plant pathogenesis-related proteins. Proteins involved in cell wall remodeling for pollen tube growth include expansins, calcium-binding allergens, and pectate lyase for degradation of pectin in the cell wall. Pathogenesis-related proteins are involved in stress or defense responses and include enzymes such as proteases and molecules such as defensins. It is thought that enzymatic allergens, particularly proteases, increase allergenic sensitization (Stewart et al. 2009). A variety of air-sampling methods are available to characterize the type and number of pollen grains found in outdoor air. It is estimated that 30 pollen grains per cubic meter of air is needed to elicit an IgE-mediated reaction (Volcheck 2009). During problematic allergenic seasons for a patient, the amount of allergen exposure required to elicit a response can decrease due to concurrent inflammation. This phenomenon is known as priming (Wallace et al. 2008). The prevalence of particular pollen grains is dictated by geographic area and can vary quite widely.

Structure

Light microscopy is able to identify pollen grains based on their physical characteristics. The outer layer of the grain is called the exine and has various characteristics particular to each pollen including its thickness, pores, spines, and furrows (Volcheck 2009).

Tree Pollens

Tree pollen grains are usually between 20 and 60 μm. Trees are divided into two classes: gymnosperms (seeds in cones) and angiosperms (seeds in the female parts of the flower). Gymnosperms are less important for allergy (though can be important in particular areas such as mountain cedar) and include trees such as pines, spruces, junipers, and redwood. Angiosperms are the more allergenic trees and include orders such as poplars, birches, oaks, elms, walnuts, hickories, sycamores, and maples (Brooks and Bush 2009).

Grass Pollens

Grass pollens are usually between 30 and 40 μm and usually have similar appearances to each other, and the pollen is usually released in the afternoon. A few of the wind-pollinated grasses contribute to the majority of grass-related allergic symptoms. Important grasses include Kentucky bluegrass, orchard, timothy, redtop, sweet vernal, and Bermuda grass (Brooks and Bush 2009). Most of the allergenic grasses are members of the Poaceae family and cross-react extensively with each other. Exceptions to this include Bermuda and Bahia grass (Shah and Grammer 2012).

Weed Pollens

Weeds are noncultivated plants. Important allergenic weeds include ragweed (variety of subtypes), marsh elder, cocklebur, sagebrush, mugwort, sorrel, pigweed, lamb's-quarters, Russian thistle, kochia, and English plantain. Ragweed pollen in particular is about 20 μm (Brooks and Bush 2009). Ragweed pollen is one of the most important causes of allergic symptoms in North America. A variety of species exist including short and giant ragweed. Individual ragweed plants can produce a prolific amount of pollen in excess of 1 million pollen grains per day (Shah and Grammer 2012). Ragweed pollen is usually released in the morning but does not disperse until after-ground humidity has evaporated later in the day (Volcheck 2009).

Avoidance

It is difficult to avoid specific problematic pollen allergen as wind carries pollen grains for miles.

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Weather conditions do affect pollen levels. Windy conditions promote dispersion of pollen grains as opposed to the dampening effect of rain. In addition, particular plants pollinate during specific times of the day which can produce a variable pollen count depending on the time of day (Volcheck 2009). Tree pollens tend to have shorter range of wind dispersion as compared with weeds which can be as much as hundreds of miles from its origin (Brooks and Bush 2009).

Specific aerobiology conditions affect the pollination seasons for trees, grasses, and weeds. Current and previous soil conditions and amount of light per day all play a role in pollination. Generally, trees tend to pollinate in the spring, grasses during the summer, and weeds in later summer and fall. Pollination patterns can vary quite widely depending on ambient conditions and can vary year by year for the same area. For example, grass season can be as long as 10 months or longer in areas such as Florida (Volcheck 2009). In addition, changing climate conditions associated with general average increases in temperature have impacted vegetation geographic patterns, pollen season length, and ability of plants to produce more and larger size pollen (Shah and Grammer 2012).

By identifying specific pollen allergen sensitivity in an individual and correlating symptoms with pollination patterns, allergenic people can develop an understanding of why symptoms tend to flare during particular conditions and times of year. Unfortunately, there is no way to effectively control exposure to pollen outdoors, but attempts have been made to decrease exposures.

Modifying behavior during the pollination season may help reduce exposure such as minimizing or avoiding outdoor activities during those times especially such activities as mowing and yard maintenance. Generally, pollen counts are higher on dry, hot, and windy days and tend to be lowest in the early morning and late evening or after recent rain showers. If outdoor activity is unavoidable, there might be utility in wearing a mask when outdoors. In order to reduce indoor levels of pollens, windows should be kept closed during the season with use of air-conditioning. HVAC (heating ventilation air-conditioning) systems and air-filtration units can also reduce indoor exposure to pollens. Vents should be closed in homes and cars to avoid introducing additional pollen into the environment. Also, in order to reduce continued pollen exposure, removal of clothing after being outdoors immediately, isolating it in a particular area of the house such as the laundry, and showering can reduce indoor exposure. Washing bedding more frequently during problematic seasons is recommended, as well as keeping outdoor pets out of the bedroom and washing them as well (Wallace et al. 2008; Grammer and Harris 2009; Volcheck 2009; Dykewicz and Hamilos 2010; Mucci et al. 2011; Reisacher 2011).

Cross-References

- Analytes and Biomarkers: Environmental Allergen Assessment
- Asthma Variants: Allergic Asthma
- Role of IgE in Disease

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Allergen Immunotherapy, Overview

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Synonyms

Allergen immunotherapy; Allergen-specific desensitization; Allergy immunotherapy; Allergy injections; Allergy shots; Hyposensitization; Immunotherapy

Definition

Immunotherapy is a procedure by which specific allergens are repetitively administered to individuals who are sensitized to these allergens through IgE-mediated mechanisms for the purpose of diminishing or eliminating the allergic symptoms due to these specific allergen exposures (Cox et al. 2011).

Background

Conventional subcutaneous immunotherapy has been an effective treatment option for many allergic diseases for the last 100 years (Casale and Stokes 2011). Immunotherapy is effective for pollen, animal allergens, mold/fungi, dust mite, and Hymenoptera sensitivity. In addition, there is evidence that immunotherapy might be effective for the treatment of atopic dermatitis in some individuals. Immunotherapy may also prevent the development of asthma in patients with allergic rhinitis (Cox et al. 2011).

Immunotherapy Extract Preparation and Allergen Selection

Immunotherapy has risks for serious systemic reactions including anaphylaxis. Therefore, immunotherapy extract preparation should be performed by health-care professionals appropriately trained and experienced in handling allergenic products. These health-care professionals include, but are not limited to, registered nurses, licensed practical nurses, medical technicians, medical assistants, physician assistants, advanced practice nurses, and physicians (Cox et al. 2011).

The components of an immunotherapy extract should be selected based on a careful clinical history in correlation with positive allergy skin test results or serum-specific IgE antibodies. Only clinically relevant allergens should be included in the immunotherapy extract. Studies indicate that skin testing may be more sensitive in detecting allergen-specific IgE than in vitro testing. Thus, skin testing is the preferred method for selection of allergens for inclusion in an immunotherapy extract and for determining the starting dose of an immunotherapy program (Cox et al. 2011).

When the appropriate allergen or allergens are selected, the immunotherapy extract mixture can be formulated. Factors to be considered with this formulation include cross-reactivity of allergens, optimal dose for each constituent allergen, and potential interaction between different types of allergens (Cox et al. 2011).

Immunotherapy Administration and Dosing

Immunotherapy injections should be administered subcutaneously in the lateral or posterior portion of the arm. Subcutaneous injections result in a reservoir of allergen extract that is slowly absorbed. Immunotherapy should be administered under the direct supervision of a qualified, appropriately trained health-care professional in a facility that has the appropriate equipment, medications, and personnel to treat anaphylaxis (Cox et al. 2011).

Immunotherapy administration occurs in two phases: the initial buildup phase and the maintenance phase. During the buildup phase, the dose and concentration of immunotherapy extract are gradually increased. During the maintenance

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phase, the patient receives an effective therapeutic dose of immunotherapy over time. The starting dose for the buildup phase is usually a 1,000-fold or 10,000-fold dilution of the maintenance concentrate. Lower starting doses may be considered for highly sensitive patients (Cox et al. 2011).

During the buildup phase, increasing doses of immunotherapy extract are commonly administered one to three times a week. The buildup phase can be accelerated through the use of cluster or rush immunotherapy schedules. With cluster immunotherapy, two or more injections are administered per visit. Rush schedules are more rapid than cluster immunotherapy, and maintenance doses may be achieved within hours to days. These accelerated schedules are advantageous in that therapeutic maintenance dosing can be achieved with fewer office visits in a shorter period of time. However, accelerated schedules may have an increased risk of local or systemic reactions (Cox et al. 2011).

Duration of Treatment

Clinical improvement can be demonstrated after achieving maintenance dosing. Individuals should be evaluated every 6–12 months while receiving immunotherapy to assess efficacy, monitor compliance, monitor adverse reactions, and determine if dosing adjustments are necessary. A decision about continuation of effective immunotherapy is generally made after an initial period of 3–5 years of treatment. After discontinuation of immunotherapy, many patients may experience clinical remission of their allergic disease, but others may relapse and have some symptoms return after a period of time (Cox et al. 2011).

Cross-References

- ▶ Immunotherapy for Allergic Rhinitis
- ▶ Immunotherapy for Asthma
- ▶ Immunotherapy for Hymenoptera Allergy
- ▶ Immunotherapy, Mechanisms
- ▶ Immunotherapy with Recombinant and DNA-Conjugated Allergens
- ▶ Safety of Immunotherapy
- ▶ Sublingual Immunotherapy

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Allergens in Gloves

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Synonyms

Hypersensitivity to gloves

Definition

Rubber and nonrubber gloves are a known cause of allergic contact dermatitis and contact urticaria. The most frequent cause of contact urticaria is natural latex. Contact dermatitis is a type IV hypersensitivity affection characterized by the formation of eczema in regions exposed to contact with the glove.

Allergens implied are additives used in glove production. In rubber gloves, thiuram, carba, mercapto, thioureas, and amine derivatives are the most important agents. For plastic gloves, plasticizers, bisphenol A, coloring agents, and antimicrobials have been described as cause of allergic contact dermatitis.

Introduction

Gloves are used to protect the skin from exposition to toxic or allergenic substances,

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both in occupational and domestic setting, but gloves themselves are able to produce skin disorders. Gloves allergens have been identified as causal agents in allergic contact dermatitis and allergic contact urticaria. In addition, continued use of gloves can aggravate a preexisting dermatitis and/or cause an irritant contact dermatitis.

There are three main types of gloves that are widely used and have been related with skin allergy: natural rubber latex gloves, synthetic rubber gloves, and plastic gloves. Other materials as leather and textile have been described too as source of allergens.

- **Natural rubber latex** (**NRL**) is extracted from the tree *Hevea brasiliensis*, a plant of the *Euphorbiaceae* family original from South America. It was first described by Spanish author Pedro Mártir de Anglería in his book *Décadas de Orbe Novo* in the sixteenth century. Nowadays, most of the production is aimed to car tire industry. It is used too in gloves, boots, and other articles for workers' protection.
- **Synthetic rubber gloves** are made of chloroprene (Neoprene®) or nitrile rubber.
- **Plastic polymeric gloves** are made of polyvinyl alcohol (PVA) and polyvinyl chloride (PVC). Both are a suitable alternative for NRL allergic patients, but these materials and its additives are able to cause sensitization too (Conde-Salazar 2004).

Fabrication of Natural Rubber Latex

The process of natural rubber production begins with extraction from the plant through a cut in the tree bark. Formic and acetic acids are added to coagulate the latex and the resulting material is then washed and pressed to form layers. At this stage, rubber has some elasticity and plasticity only between 15 °C and 30 °C. Then, the rubber is grinded and mixed (malaxated), molded with the desired form, and vulcanized. Vulcanizing is a polymerization process to create a crystalline three-dimensional structure which has properties as strength, elasticity, and resistance.

To accelerate the vulcanization process and to conserve its properties, a number of substances are added during the process of production. Some of these substances are responsible for most contact dermatitis to NRL gloves and are used too in the production of synthetic rubber gloves (Conde-Salazar 2004; Mellström and Boman 2005).

Epidemiology

Use of gloves between healthcare workers increased since the 1980s due to the acquired immune deficiency syndrome (AIDS) epidemic; as a consequence, hypersensitivity to NRL and other gloves compounds incidence and prevalence increased.

Rubber gloves are the main occupational and nonoccupational source of allergy to rubber. They are responsible for 40–70 % of occupational contact dermatitis due to rubber sensitization (Wahlberg and Maibach 2005). A recent multicenter study conducted in Central Europe concluded that 24 % of patients who were studied because occupational contact dermatitis presented sensitization to rubber gloves compounds. From them, 30.7 % were healthcare workers, 7.6 % cleaning workers, 7.3 % worked in industry, and 5.3 % were hairdressers. Thiuram group was the more prevalent allergen, responsible for sensitization in 12.2 % of the study population and up to 15 % of health workers (Geier et al. 2012).

Clinical Manifestations

NRL gloves are implied in both type I (contact urticaria, anaphylaxis) and type IV (contact dermatitis) hypersensitivity. Type I NRL allergy is described in other section of this work (see ► Sensitization and Allergy to Natural Rubber Latex) so the present chapter focuses mainly on allergic contact dermatitis (ACD) caused by gloves compounds in NRL, synthetic rubber, and plastic gloves.

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1. **Contact Dermatitis**
   Most frequent clinical manifestation is eczema. It is an inflammatory disease in the skin engaging the epidermis. It entails one or several of the following morphological changes: erythema, edema, papules, and vesicles. Commonly it also may be scaly, encrusted, oozing, and lichenified.

   Allergic contact dermatitis is caused by a delayed hypersensitivity mechanism (type IV of Gell and Coombs classification) to an allergen through which is directly contacting with the skin. When gloves are the responsible agents, it is usually delimitated to the hands, although it may affect other body parts as genitals, face, or flexures, mainly due to use of gloves for manipulating this regions.

   Eczema characteristics may vary depending on the affected area, time of evolution, and previous treatments. As in any eczema, the elemental lesion is the vesicle, with exudation and scarification in most acute forms and/or delicate skin localizations and hyperkeratosis and lichenification in more chronic forms and thicker skin regions.

   Antioxidants amines have been associated to a keratosis form affecting palms and plants (when using rubber boots) called "hands and feet of the black rubber."

   Other specific type is the PPP syndrome. It is an allergic dermatitis with apparition of purpura, petechiae, and pruritus, caused by antioxidant amine *N*-isopropyl-*N*-phenyl-p-phenylenediamine (IPPD) (Conde-Salazar 2004).
2. **Contact Urticaria**
   It is characterized by the apparition of hives, erythema, and itching in the hands in a few minutes after wearing the glove. The most frequent allergen implied is NRL, but some accelerators of rubber gloves, plasticizers, and other gloves compounds (casein and corn starch) have been identified as cause of contact urticaria (Rose et al. 2009).
3. **Proteinic Contact Dermatitis**
   It is a mixed type I and IV hypersensitivity pathology. Clinic is characterized by a chronic dermatitis with immediate exacerbations when contacting with the allergen. It most frequently caused by NRL (Garcés-Sotillos et al. 2007).

Allergens in Rubber Gloves

Vulcanizing Accelerators

They are products added to the NRL and synthetic rubber to catalyzing the vulcanizing process and allowing performing it at lower temperatures and in less time. This group includes some of the more frequent causes of glove-induced contact dermatitis:

– Thiuram Group
  It is still the most common agent causing delayed hypersensitivity to gloves. It is used for NRL and synthetic rubber gloves. Most rubber products contain one or more of them. They may be present too in other products as adhesives, painting, lubricants, soap, antioxidants, and antifungic agents.

  The most frequent sensitization agent in thiuram group is tetraethylthiuram disulfide (TETD). It is included in the "thiuram mix" preparation for patch testing. Other components of this group are tetramethylthiuram monosulfide (TMTM), tetramethylthiuram disulfide (TMTD), and dipentamethylenethiuram disulfide (DPTD) (Conde-Salazar 2004; Rose et al. 2009).
– Dithiocarbamates
  Most frequent sensitizers in this group are zinc diethyldithiocarbamate (ZDEC) and zinc butyldithiocarbamate (ZBDC). Both are included in the "carba mix" for patch testing and are frequently associated with rubber gloves contact dermatitis. Dithiocarbamates can be found also in fungicides, pesticides, and other rubber products as condoms and elastics in clothes (Conde-Salazar 2004).
– Iodopropynyl Butylcarbamate (IPBC)
  It is a preservative used in industrial preparations and personal care products, but there is no evidence of cross-reactivity with ZDEC and ZBCD (Warshaw et al. 2013a). In cross-reactivity between dithiocarbamates and thiuram group that could be explained by

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chemical structure similarities. However, other authors talk about concomitant sensitization to both substances (Rose et al. 2009).

- Thiazole group
  It is known also as mercapto group. It includes substances from the benzothiazole and the sulfonamide family. Mercaptobenzothiazole (MBT) and dibenzothiazyldisulfide (MBTS), in the benzothiazole group, and *N*-cyclohexyl-2-benzothiazylsulfenamide (CBS) and morpholinylmercaptobenzothiazole (MOR), in the sulfonamide family, have been identified as relevant allergens.

  MBT alone and a "mercapto mix" (MBTS, MOR, and CBS) are used in the patch testing for rubber dermatitis diagnosis (Conde-Salazar 2004; Rose et al. 2009). A recent study has concluded that MBT alone could be enough to diagnose most patients sensitized to mercapto group, as the "mercapto mix" could be useful in auxiliary rubber series (Warshaw et al. 2013b).
- Thioureas
  They are used as accelerators especially in manufacture of neoprene. Gloves have been found to be the most common occupational source of allergic contact dermatitis to thioureas although they have been also found in tourniquets, rubber clothes, sport shoes, swimming glasses, cleaning products, fungicides, tires, and photocopy and photographic paper.

  The most important agents in this group are dibutyl thiourea and diphenyl thiourea. Thioureas are not always included in standard patch testing series so the suspect is important for diagnosis (Conde-Salazar 2004; Rose et al. 2009; Kohli and Habbal 2010).

Retarders

Substances used in the rubber industry to slow the process of vulcanization. They are not a frequent source of sensitization because they are usually washed off during the production process. However, positive patch tests to cyclohexylthiophthalimide have been found in some patients with allergic contact dermatitis caused by gloves (Rose et al. 2009).

Antioxidants

These groups of chemicals are added to rubber to inhibit rubber degeneration by oxygen and ozone. Antioxidants from amine group are the most effective in rubber production and are widely used. They usually blacken the rubber and are used mainly in industry applications as work gloves, boots, tires, hoses, and rubber components of machinery and electro domestics. Most of these substances are paraphenylenediamine derivatives. P-phenylenediamine is a potent sensitization agent that is present also in hair dyes and is an important cause of occupational and nonoccupational contact dermatitis both in hairdressers and users of dyes. Antioxidants amines are released to the surface of the glove with heat and rubbing. They have high sensitizing ability. In this group we can find isopropylphenylenediamine (IPPD), *N*-cyclohexyl-*N*′ phenyl-paraphenylenediamine (CPPD), and *N*, *N*-diphenyl-p-phenylenediamine (DPPD). Other antioxidants with allergenic activity are butylated hydroxyanisole (BHA), methylcyclohexyldimethylphenol, and 4, 4′-thiobis (6-tert-butyl-meta-cresol) (Lowinox® 44S36) (Conde-Salazar 2004; Rose et al. 2009).

Antimicrobials

Cetylpyridinium chloride is a quaternarium ammonium compound which is used as an antimicrobial in some gloves. It has been implicated in some reports of contact dermatitis caused by gloves (Rose et al. 2009).

Natural Rubber Latex

Although it is a major cause of type I hypersensitivity, NRL itself has been reported as a cause of delayed hypersensitivity in at least two patients with contact dermatitis caused by gloves and positive patch tests only for NRL (Rose et al. 2009).

Allergens in Plastic Gloves

Polymers

Various polymers are involved on the manufacture of plastic gloves, including polyvinyl

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chloride (PVC), polyvinyl alcohol (PVA), polyethylene, and polyvinyl acetate. The addition of different chemicals during production often introduces potential allergens.

Plasticizers

Plasticizers are compounds added to plastics in small amounts (<5 %) to harden them or in large amounts to soften them. There have been isolated reports of allergic contact dermatitis caused by the plasticizers adipic polyester and polyadipic acid-co-1,2-propylene glycol, associated also, in the latter case, with positive patch testing to the stabilizer di-(n-octyl) tin-bis(2-ethylhexylmaleate) (Sowa et al. 2005; Ueno et al. 2007).

A further group of plasticizers are the epoxy resins, used in the manufacture of PVC gloves. Although there are no reported cases of glove allergy secondary to epoxy resins in plastic gloves so far, they remain a potential allergen.

There is a case report of one patient with delayed hypersensitivity to plastic gloves who had positive patch test reactions to the components tricresylphosphate, triphenyl phosphate, and methyldichlorobenzenesulfonate from the plastics and glue series, but the relevance of these results is uncertain (Estlander et al. 1986).

Plasticizers have been also related with contact urticaria. Several cases have been recorded secondary to the plasticizer di(2-ethylhexyl) phthalate in PVC gloves and in polyethylene gloves, but in the latter case the patient also had positive prick testing to octadecanoic acid methyl ester, 2,6-di-tert-butylphenol, *cis*-13-docosenoic acid amide (Erucamide), and octadecyl 3-(3,5-di-tert-butyl-4-hydroxyphenyl) propionate (Irganox® 1076). Authors could not determine which was the most likely allergen (Rose et al. 2009).

Antioxidants

Bisphenol A is used as an antioxidant and as an inhibitor of end polymerization in the manufacture of PVC gloves. It is a rare allergen, but there are several reports of contact allergy in the setting of PVC glove use (Matthieu et al. 2003; Aalto-Korte et al. 2003).

Antimicrobials

There have been several reports about patients found to be allergic to the antimicrobial agent 1,2 benzisothiazolinone (Aalto-Korte et al. 2007, 2006), only present in certain powder-free PVC gloves.

Formaldehyde has been found to be the underlying cause in one patient with glove allergy (Ponten 2006). It has been suggested that formaldehyde may be added to the gloves during manufacture either as such or in the form of a formaldehyde releaser.

Coloring Agents

Only a few cases of contact dermatitis secondary to coloring agents have been reported. The allergens implicated were the colorant Irgalite Orange F2G (Pigment Orange 34, C.I. 21115) and the blue pigment Vinamon® Blue BX FW, a phthalocyanine blue in a vinyl glove (Rose et al. 2009).

Allergens in Leather Gloves

Chromium (III) sulfate is used in the tanning process of the leather and may be oxidized during this procedure to form chromium (VI), a potent, highly bioavailable contact allergen. Chromate allergy is well recognized in occupational leather exposure, and there are specific reports of leather glove allergy (Fregert and Gruvberger 1979). Following tanning, chromium (III) is bound to collagen resulting in a lower bioavailability and is therefore less likely to elicit contact dermatitis, but studies suggest that it may also play a role. Chromate is released when leather gloves become moist and this can result in delayed hypersensitivity. Significant levels of chromium (VI) have been detected in a number of leather products, including protective gloves (Hansen et al. 2002). Nonetheless, European standards stipulate the requirement for chromium (VI) to be undetectable.

Allergens in Textile Gloves

There is an isolated report of textile dyes resulting in delayed hypersensitivity through the

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use of protective gloves, in contrast to the relatively common occurrence of textile dye contact dermatitis resulting from other clothing. In this case, there were positive reactions to Disperse Orange 3, Acid Red 118, Direct Orange 34, Dispersed Red 17, Disperse Blue 35, Disperse Orange, and 4-aminoazobenzene (Rose et al. 2009).

Diagnosis

The diagnosis is based upon a combination of clinical features (morphology, location, and symptoms) of the eruption; history of exposure to a putative allergen during work, hobbies, or home activities; patch testing results; and lack of recurrence after empirical treatment of the dermatitis and avoidance of the suspected allergen.

Correctly identifying the underlying mechanism of a glove-related reaction using patch tests can be difficult because in some individuals' symptoms of both type IV and type I allergic reactions may be present (Conde-Salazar 2004). All of the rubber accelerators should be tested by patch testing. Latex allergies which present as hives are best tested by prick or scratch testing and this is performed by an allergist.

Allergens considered to form a basis for patch testing patients with suspected delayed hypersensitivity to gloves are included in Table 1 (adapted from Rose et al. 2009).

In addition, it is important to patch test with material from the glove. Typically, this would be with a piece of glove material cut from the glove and applied under occlusion. False-positive reactions may occur secondary to pressure from the glove material underneath the patch, but these must be interpreted in light of the patient's history. Although it is possible to produce solvent-based extracts for the purpose of patch testing, this is likely only to be available in a limited number of centers.

If delayed hypersensitivity to latex is suspected, accelerator-free latex fluid is requested from the manufacturer and is also tested.

Finally, if results are equivocal, then a "glove use test" may be performed. The patient wears the gloves for 2 h. daily over 3 days and is then assessed (Rose et al. 2009). This, however, would not distinguish between allergic and irritant contact dermatitis. Compound allergy is a theoretical explanation for the presence of a positive patch test to a finished product despite negative reactions to individual ingredients themselves (Rose et al. 2009) and may occur due to manufacturing processes. Compound allergy in gloves should be detected using the glove use test. It is also useful to consider a use test for investigating glove-related contact urticaria if prick testing/specific IgE for suspected allergens is negative, but the history is suggestive. The patient wears the glove for 20 min in an observed setting to ensure that any resulting urticaria is not dermographism secondary to scratching (Rose et al. 2009). A control glove is worn on the other hand.

In patients with suspected contact urticaria to gloves, several chemicals might be suggested for prick testing, including latex, casein, corn starch powder, zinc diethyldithiocarbamate, morpholinylmercaptobenzothiazole, and di(2-ethylhexyl) phthalate.

Prevention

For practical purpose, protective gloves can be classified into different types according to use and thickness:

- Type I: disposable gloves (thickness, 0.007–0.25 mm)
- Type II: household gloves (thickness, 0.20–0.40 mm)
- Type III: industrial gloves (thickness, 0.36–0.85 mm)
- Type IV: special gloves

Gloves can also be classified by weight in ultra/very light weight (<0.20 mm) or light weight (0.20–0.31 mm), medium weight (0.31–0.46 mm), and heavy weight (>0.46 mm). Protective gloves can be made of rubber and plastic materials, leather, textile, and combinations of these materials. The quality can differ due to manufacturing processes and additives (Mellström and Boman 2005).

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Allergens in Gloves, Table 1 Allergens considered for patch testing in patients with suspected contact dermatitis to gloves

Source of allergen	Allergen	Patch test
Baseline series (a) not in European baseline series	Mercaptobenzothiazole	2 % pet
	Potassium dichromate	0.5 % pet
	Carba mix [(a)]	3 % pet
	Thiuram mix	1 % pet
	Formaldehyde	1 % aq
	N-isopropyl-*N*′-phenyl-paraphenylenediamine	2 % pet
	Mercapto mix	0.1 % pet
	Epoxy resins	1 % pet
Rubber series	*N*-Cyclohexyl-2-benzothiazylsulfenamide	1 % pet
	Morpholinyl mercaptobenzothiazole	0.5 % pet
	Dibenzothiazyl disulfide	1 % pet
Thiuram mix	Tetraethylthiuram disulfide	0.25 % pet
	Tetramethylthiuram monosulfide	0.25 % pet
	Tetramethylthiuram disulfide	0.25 % pet
	Dipentamethylenethiuram disulfide	0.25 % pet
Carba mix	Zinc diethyldithiocarbamate	1 % pet
	Zinc dibutyldithiocarbamate	1 % pet
	Zinc dimethyldithiocarbamate	1 % pet
	1,3-Diphenylguanidine	1 % pet
Black rubber mix	*N*-cyclohexyl-*N*′-phenyl-paraphenylenediamine	1 % pet
Thioureas	Dibutyl thiourea	1 % pet
	Diphenyl thiourea	1 % pet
	Diethyl thiourea	1 % pet
	Dialkyl thiourea mix	1 % pet
	Butylated hydroxyanisole (BHA)	2 % pet
	1,2 Benzisothiazolinone	0.05 % pet
	4,4-Dihydroxydiphenyl ether	0.1 % pet
Plastic and glue series	Bisphenol A	1 % pet
Noncommercially available allergens	4,4′-thio*bis* (6-*tert*-butyl-*meta*-cresol)	1 % pet
	Cetyl pyridinium chloride	0.1 % aq
	Adipic polyester	5 % pet
	Poly(adipic acid-*co*-1,2-propylene glycol)	5 % pet
	Di-(*n*-octyl) tin-bis(2-ethylhexylmaleate)	1 % pet
	Methylcyclohexyldimethylphenol	1 % pet

If patients are found to have a positive patch test or prick test to a glove allergen, they must obviously avoid the identified allergen while continuing to use a glove which offers appropriate protection. Glove manufacturers publish guidance on the permeation (i.e., the passage of chemicals through the glove material) and degradation (i.e., the reduction in the physical properties of the glove as a result of exposure to given chemicals) qualities of glove. This information aids determination of the most suitable glove for use in specific conditions. In response to the growing interest in allergic contact dermatitis, several glove manufacturers have introduced accelerator-free products. Some glove brands carry the claim low dermatitis potential, which is regulated by the Food and Drug Administration (FDA) (Table 2) (www.research.northwestern.edu 2012).

Also, there are some recommendations from the American Latex Allergy Association, the

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Allergens in Gloves, Table 2 Low dermatitis potential gloves

Glove materials	Brand names	Accelerators
Polyisoprene	Derma Preen, IsoTouch (Ansell)	Carbamates or thiurams
	Biogel (Biogel/Molnlycke Health Care)	Thiazoles
	Esteem (Cardinal Health)	
	Sensicare (Medline Industries)	
Vinyl (polyvinyl chloride)	Dura-Touch/Trutouch (Ansell, Maxxim)	No accelerators
	Triflex (Allegiance)	ACD rarely been reported
Nitrile (butadiene copolymer)	Safeskin (Safeskin Corp.)	Carbamates
	Sensi Care (Maxxim Medical)	Thiazoles
	Tillotson Pure Advantage and Dual Advantage (Tillotson)	
	Smart Care (SmartCare, Inc.)	
	Allegiance Flexam Nitrile Examination Glove (Allegiance)	
	Adenna NPF Nitrile Powder Free Exam Gloves (Adenna Inc.)	
Nitrile (butadiene copolymer) accelerator-free	True Advantage (Tillotson)	No accelerators
	N-Dex (Ansell, Best Glove)	
	Aspen 2100 (Hourglass Indust.)	
	Semper Sure (Sempermed)	
Neoprene (polychloroprene polymer)	Derma Prene (Ansell)	Thiourea
	Biogel Neoprene; Duraprene (Allegiance)	Diphenyl guanidine
	Neolon (Maxxim)	Carbamates
Polyurethane	Sensi Care (Maxxim Medical)	No accelerators
Styrene butadiene block polymer	Elastyren (ECI Medical Technologies)	No accelerators
	Aller Gard (AllerGard)	

National Institute for Occupational Safety and Health, and the Office for Research Safety (ORS):

- Latex gloves should be used only as mandated by accepted universal precautions standards. The routine use of latex gloves in low-risk situations should be discouraged.
- Only low-allergen latex gloves should be purchased and used.
- Only powder-free latex gloves should be purchased and used.
- If you have or suspect allergic reactions to a glove material, consult your physician or the ORS.

Cross-References

- ▶ Allergic Contact Dermatitis
- ▶ Contact Dermatitis Due to Thiourea Derivatives
- ▶ Protein Contact Dermatitis
- ▶ Sensitization and Allergy to Natural Rubber Latex
- ▶ Textile Allergy

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Allergic Bronchopulmonary Aspergillosis

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Definition

Allergic bronchopulmonary aspergillosis (ABPA) is a hypersensitivity reaction characterized by recurrent episodes of worsening obstructive lung disease, mucoid impaction, and increased respiratory symptoms in patients who have either asthma or cystic fibrosis (CF), are sensitized to *Aspergillus fumigatus*, and meet established diagnostic criteria.

Background

Aspergillus fumigatus is a ubiquitous mold that is found both indoor and outdoor. It is present in the air we breathe but also in soil and other outdoor environments that are predisposed to the growth of mold, such as decaying vegetation and mulch, as well as in humid areas like crawl spaces, compost piles, and sewage treatment facilities (Slavin et al. 1988; Paris et al. 1997). In addition to ABPA, which is discussed below, *A. fumigatus* can contribute to several pulmonary conditions, such as atopic asthma, hypersensitivity pneumonitis (see separate entry), or invasive disease as is seen in invasive aspergillosis and aspergillomas. Invasive aspergillosis affects patients who are immunocompromised and involves invasion by aspergillus of the lungs, bone, or central nervous system (CNS). Aspergillomas, on the other hand, develop in patients with preceding pulmonary disease such as cancer or another cavitary lesion, which predisposes them to the focal growth of aspergillus, leading to formation of a fungal ball in the cavity. Both invasive aspergillosis and aspergilloma require systemic antifungal

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Allergic Bronchopulmonary Aspergillosis, Table 1 Diagnostic criteria in patients with asthma (Data references: Greenberger 2002; Greenberger and Patterson 1986; Akuthota and Weller 2012)

	Major criteria: asthma	ABPA-S (seropositive)	ABPA-CB (central bronchiectasis)
Asthma history	✓	✓	✓
Immediate skin test reactivity to *A. fumigatus*	✓	✓	✓
Precipitating IgG antibodies (precipitins) against *A. fumigatus*	✓	✓	
Total IgE ≥417 IU/mL (or ≥ 1,000 ng/mL)	✓	✓	✓
Infiltrates	✓		
Peripheral blood eosinophilia (>500/mm^2)	✓		
Specific IgG elevated against *A. fumigatus*	✓		✓
Specific IgE elevated against *A. fumigatus*	✓		✓
Central bronchiectasis on chest CT scan	✓		✓

therapy, and aspergilloma generally also requires surgery to remove the abnormal portion of the lung so that the aspergilloma does not continue to form (Knutsen and Slavin 2011).

Allergic bronchopulmonary aspergillosis (ABPA) is a pulmonary disease that occurs due to colonization by *A. fumigatus* in a sensitized host, that is, in someone who is allergic to *A. fumigatus*. Other than displaying allergic sensitization to *A. fumigatus*, a person must also carry a diagnosis of asthma or CF in order to develop ABPA. ABPA affects approximately 2–32 % of patients with asthma and 1–15 % of patients with CF (Stevens et al. 2003; Agarwal et al. 2009). Although other molds can cause a similar condition, termed allergic bronchopulmonary mycosis (ABPM), *A. fumigatus* is the most common mold responsible for this type of disease process.

Clinically, ABPA generally causes flares of underlying asthma or CF and is accompanied by mucus plugging, worsening obstructive lung disease, fever, malaise, peripheral blood eosinophilia, and coughing up of brownish mucus plugs.

Diagnostic Approach

The diagnostic criteria for ABPA, which is shown in Table 1, differ between patients with classic ABPA and its two variants, ABPA-S (seropositive) and ABPA-CB (central bronchiectasis).

Because allergic sensitization to *A. fumigatus*, elevated total IgE levels and eosinophil counts, positive serum precipitins against *A. fumigatus*, and mucus plugging can be seen in all patients with moderate to severe asthma, ABPA can be a difficult diagnosis to make. It should be suspected in patients with allergic asthma who have difficulty controlling their asthma or are having recurrent flares, as well as in patients with eosinophilic lung disease and/or bronchiectasis. In addition, the index of suspicion should be high in CF patients with an elevated total IgE level. The classic and minimal criteria for a diagnosis of ABPA in patients with CF are shown in Table 2 below.

Clinical Course

There are five stages of ABPA (Table 3), but every patient with ABPA does not necessarily go through all five stages, and the stages need not fall in sequential order.

A given patient can bounce in and out of a given stage, particularly as they alternate between exacerbations and remission. Although not based in controlled studies, the current recommendation is for aggressive treatment of early stage disease as a way of potentially halting or slowing the development of bronchiectasis and/or fibrosis as seen in stage V disease. It is thought that the inflammation associated with acute

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Allergic Bronchopulmonary Aspergillosis, Table 2 Diagnostic criteria in patients with cystic fibrosis (Data taken from Stevens et al. 2003)

Diagnostic feature	Classic criteria for ABPA-CF	Minimal criteria for ABPA-CF
Cystic fibrosis	✓	✓
Acute or subacute clinical deterioration with no other cause	✓	✓
Sensitization to *A. fumigatus* by positive immediate skin test reactivity or elevated specific IgE	✓	✓
Total IgE level[a]	≥ 1,000 IU/mL (≥ 2,400 ng/mL)	≥ 500 IU/mL (≥ 1,200 ng/mL)[b]
Elevated specific IgG or precipitins against *A. fumigatus*	✓	+/− (necessary only if no infiltrates)
Infiltrates or *A. fumigatus* precipitins	✓	+/− (necessary only if no specific IgG or precipitins)

[a]If patient is taking oral steroids, repeat once patient is off of steroids
[b]If total IgE is between 200 and 500 IU/mL (480–1,200 ng/mL), repeat testing in 1–3 months

Allergic Bronchopulmonary Aspergillosis, Table 3 Clinical stages of ABPA (Data from Patterson et al. 1982)

Stage	Clinical state	Infiltrates	Total IgE level
I	Acute	Upper or middle lobe	Very high
II	Remission	None despite being off prednisone > 6 months	Normal or high
III	Exacerbation	Upper or middle lobe	Very high
IV	Steroid-dependent asthma	None or only intermittent	Normal or high
V	End stage	Fibrosis, bullous, or cavitary lesions	May be normal

ABPA and/or ABPA exacerbations may lead to progressive lung injury that eventually culminates in these anatomic changes.

Management

The mainstay of ABPA therapy is systemic corticosteroids, which work well but are unfortunately associated with several potential long-term side effects, including immunosuppression, osteoporosis, and adrenal suppression, among others. In the setting of an acute ABPA flare, a dose of 0.5–1.0 mg/kg of prednisone is an appropriate starting dose for the first 2 weeks of treatment. The dose is then weaned over the next 3–6 months, ideally with every other day dosing. To monitor a patient's progress during treatment, one can check total IgE levels on a monthly to bimonthly basis. A 35 % reduction in total IgE level for those patients starting out with a level ≥ 2,500 IU/mL (≥ 6,000 ng/mL) is generally indicative of clinical improvement and resolution of infiltrates on imaging. Ideally, patients can taper off of their steroids and remain in remission. If they are unable to stay free of clinical disease without systemic steroids, they are considered to have stage IV disease, as detailed above. Exacerbations, generally marked by symptomatic worsening, at least a doubling of the IgE level from baseline, and/or radiologic features of worsening disease, should be treated with a systemic steroid burst and taper, the duration of which will vary by patient (Akuthota and Weller 2012).

Steroid-sparing agents for ABPA include antifungal agents and anti-IgE therapy with omalizumab, although neither has been studied extensively. The use of itraconazole as an adjunct to systemic steroids is supported by two randomized trials, a retrospective cohort study, and a small prospective study (Wark et al. 2003, 2004; Pasqualotto et al. 2009; Salez et al. 1999; Stevens et al. 2000). Another antifungal agent that has shown success in the treatment of ABPA is voriconazole, which may be better tolerated than itraconazole in some patients

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and has a better bioavailability, although data backing its use is even more scarce (Glackin et al. 2009; Erwin and Fitzgerald 2007). The evidence for omalizumab comes mostly from case reports in CF patients with ABPA, although more recently a yearlong open-label study of omalizumab in 16 ABPA patients without CF demonstrated a decrease in asthma exacerbations and steroid dose as compared to the year prior to omalizumab therapy (Tillie-Leblond et al. 2011).

Cross-References

- ▶ Allergen Avoidance: Fungi and Mold Avoidance
- ▶ Analytes and Biomarkers: IgE
- ▶ Analytes and Biomarkers: Precipitin Antibodies
- ▶ Diagnostic Components: Allergen for In Vivo (Skin Testing, Immunotherapy) and In Vitro (Serology) IgE Antibody Testing
- ▶ Diseases in DDx of Asthma: Differential Diagnosis of Asthma
- ▶ IgE Testing
- ▶ mAbs (Omalizumab)
- ▶ Specific IgE

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Allergic Contact Dermatitis

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Synonyms

Allergic contact eczema

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Definition

Allergic contact dermatitis is a skin inflammation mediated by hapten-specific T-cells that elicit a delayed-type hypersensitivity and can present as acute, subacute, or chronic contact dermatitis.

Epidemiology and Risk Factors

The prevalence of contact allergy is rising worldwide. About 15–20 % of the general population in Europe is sensitized to at least one contact allergen. Most common allergens are nickel and fragrances (Peiser et al. 2012). Workplace exposure, sex, age, and genetic predispositions (atopy) were identified as most important risk factors. Women are twice as frequently affected as men, probably due to hormonal influences. In occupational contact dermatitis, the highest incidence is found among metal workers and hairdressers (Dickel et al. 2001; Peiser et al. 2012).

Pathophysiology

Allergic contact dermatitis is mediated by a cascade of three immune processes, a sensitization, an elicitation, and a resolution phase (Fig. 1). Allergens provoking allergic contact dermatitis are small molecules, called haptens. Since haptens are too small to be recognized by the immune system (molecular weight of usually <1,000 Da), their allergic potential is mediated through binding on skin-derived proteins. According to the "danger model" (Matzinger et al. 1998), haptens activate cells of the innate immunity localized in the skin and thus deliver signals that induce the recruitment, migration and maturation of antigen-presenting cells. In this context, contact allergens were shown to trigger toll-like receptor 4 and P2 × C7 signalling and to induce oxidative stress (Esser et al. 2012, Weber et al. 2010). Subsequent reactions are orchestrated by inflammatory cytokines, chemokines, and adhesion molecules (e.g., IL-18, IL1-ß, TNFα, GM-CSF).

After uptake by antigen-presenting cells, the hapten-protein complex is processed and presented at the cell surface in association with MHC class I/II molecules to T-lymphocytes in the regional lymphnodes (sensitization phase) (Vocanson et al. 2009). Cell types functioning as antigen-presenting cells in ACD are dendritic cells, mainly the epidermal langerhans cells, but also dermal dendritic cells, macrophages, keratinocytes and mast cells are involved. Co-stimulating surface marker like CD80 (B7-1), CD86 (B7-2), and ICAM-1 are expressed on the allergen-presenting dendritic cells which lead to an efficient activation of the effector T-cells.

While the sensitization phase lasts around 10 days and is usually not accompanied by clinical symptoms, re-exposure of sensitized individuals to the same hapten leads to the appearance of allergic contact dermatitis within 24–72 h (elicitation phase). Allergen-specific T-lymphocytes are recruited to the skin via the release of inflammatory mediators by resident cutaneous cells re-exposed to the hapten. The main effector T-cells are CD8+ cytotoxic T-cells that induce keratinocyte apoptosis via Fas/Fas-L and perforin/granzyme cytolytic activities. This inflammatory reaction persists for only a few days and rapidly decreases following downregulating mechanisms in the resolution phase, if the allergen is not re-applied to the skin. FoxP3-positive CD4+ CD25+ regulatory T-cells inhibit both the expansion of the allergen-specific T-cells in the lymphoid organs and their activation in the skin (Dubois et al. 2003; Cavani et al. 2001).

Clinical Features

Allergic contact dermatitis develops mostly on hands, feet and eyelids. In sensitized patients, it occurs 24–96 h after contact with the allergen. The clinical aspect depends on the disease stage. In the acute phase, it consists of erythema and edema, often followed by small itching vesicles containing clear fluid (Fig. 2).

The chronic phase is characterized by erythematous, infiltrated plaques, scaling, and

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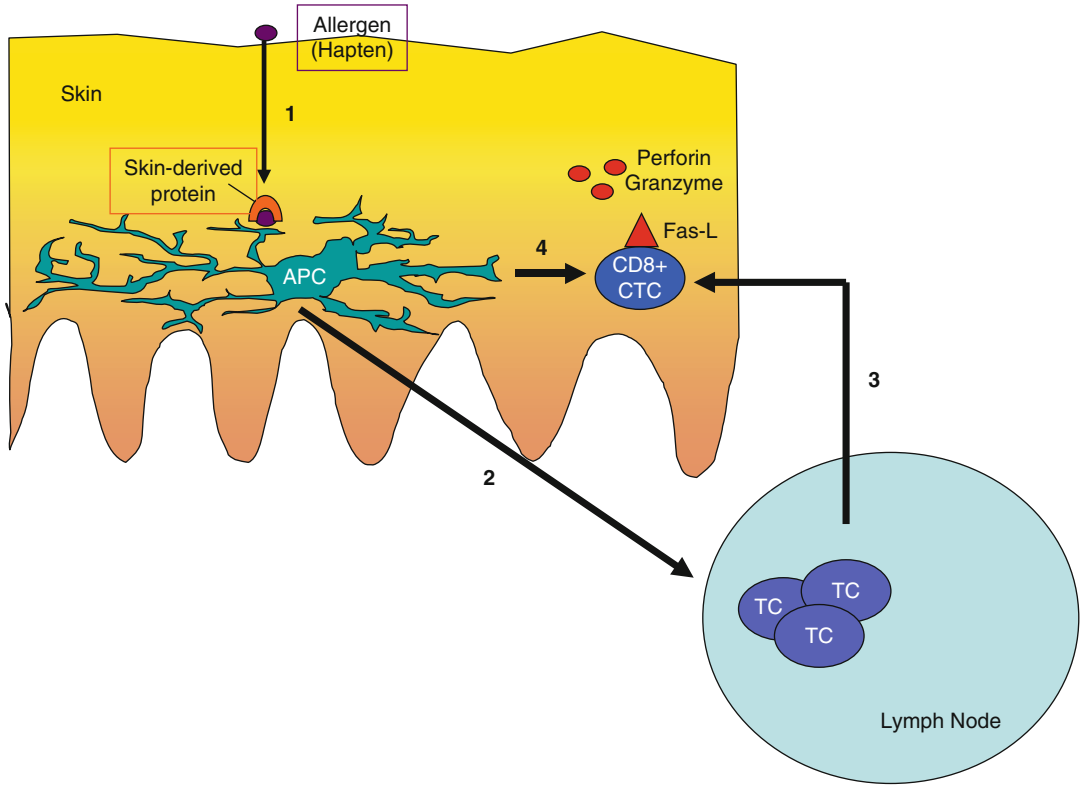

Allergic Contact Dermatitis, Fig. 1 Pathophysiology of allergic contact dermatitis (sensitization phase = 1,2,3; elicitation phase = 1,4). The allergen enters the skin as a hapten (*1*), which is bound by skin-derived proteins to become an antigen recognized by the immune system. It is taken up and processed by antigen-presenting cells (*APC*), which become activated and migrate to the regional lymph nodes (*2*). There, the allergen is presented to T-cells, which differentiate into allergen-specific T-cells and locate as memory T-cells to the skin (*3*). After repeated allergen contact (*1*), skin-residing allergen-specific *CD8+* cytotoxic T-cells (*CTC*) become activated secreting cytolytic enzymes (perforine and granzyme B) and expressing Fas-Ligand (*FasL*), which binds to Fas-expressing keratinocytes (*4*). This will lead to tissue inflammation resulting in clinically apparent dermatitis

lichenification (Gutermuth et al. 2005) (Fig. 3). In contrast to non-allergic, irritant contact dermatitis, the skin lesion can spread locally or even show satellite lesions at a distance. Irritant contact dermatitis (e.g., caused by wet work and occlusive rubber gloves) often precedes allergic contact dermatitis. Other potential risk factors are atopy, stasis dermatitis, and multisensitization (Brasch et al. 2006).

Diagnosis

Diagnosis is based on history and patch testing. History of patients should include previous dermatitis, time course, and aggravating and contact factors. Clinical features and distribution pattern may indicate the cause of contact dermatitis. The gold standard for the detection of the causative contact allergen is the allergen provocation test in form of patch testing, which reflects the elicitation phase of allergic contact dermatitis.

Therapy

The first step is the elimination of the causative contact allergen. Anti-inflammatory therapy includes the topical application of potent

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Allergic Contact Dermatitis, Fig. 2 Acute contact dermatitis of the feet with erythema, edema, and small vesicules (note that acute allergic contact dermatitis of the hands and feet usually first affects the dorsal aspect since allergen penetration is more pronounced than through the thickened corneal layer of the palms and soles)

Allergic Contact Dermatitis, Fig. 3 Chronic contact dermatitis of the hand with scaling, infiltration, and lichenification

corticosteroids and UV-light therapy in more severe cases. In case of widespread contact dermatitis, a systemic therapy with steroids (e.g., prednisone) can be indicated for a short period of time. Additionally H1-antihistamines may be administered to reduce itch. In chronic and refractory hand eczema, ciclosporin or alitretinoin, a retinoid with additional anti-inflammatory properties is also a treatment option (Diepgen et al. 2012).

Cross-References

- ▶ Emergent Allergies in Cosmetics
- ▶ Contact Allergy to Hair Dyes
- ▶ Dendritic Cells
- ▶ Diagnostic Components: T Helper Cell Cytokines (IL-4, IL-5, IL-9, IL-10, IL-13, IL-17)
- ▶ 3-dimethylaminopropylamine (DMAPA), Allergic Contact Dermatitis to
- ▶ Nickel Allergic Contact Dermatitis

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Allergic Contact Dermatitis from Exotic Woods

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Synonyms

Woods, allergic contact dermatitis from; Woods, occupational contact dermatitis from

Definition

Exotic woods come from tropical and subtropical regions of South America, South Asia, and west and central Africa. Tropical woods are beautiful, strong, stable, and resistant to moisture and fungi (Hausen 1986). They are used in the manufacture of decorative items, furniture, tool handles, musical instruments, and jewelry, occupationally and recreationally by woodworkers and hobbyists.

Sawdust of exotic woods may be irritating to the skin, eyes, nose, and lungs and in addition can cause sensitization. Most dermatoses from contact with woods are occupational and are observed in carpentry or wood industry workers. Less commonly, the finished product, such musical instruments, necklaces, or bracelets, may be responsible for dermatitis (Le Coz and Ducombs 2006).

Clinical Manifestations

Dermatitis due to wood contact is more commonly an irritant or phototoxic reaction, but exotic woods may cause allergic and photoallergic contact dermatitis and contact urticaria (Le Coz and Ducombs 2006). Less commonly, contact with wood can also result in erythema multiforme-like reactions (Veien and Hausen 2000), pigmented contact dermatitis (Pires et al. 1999), and lymphomatoid contact dermatitis (Ezzedine et al. 2007). In most cases, allergic contact reaction is a type IV allergy, but exceptionally woods can also cause type I allergy (Alvarez-Cuesta et al. 2004). Woods are known to cause occupational asthma (Jaakkola et al 2003).

Allergic contact dermatitis typically occurs after contact with fine dust particles. Sawing, machining, and turning of wood produce fine dust, and woodworkers are highly exposed to sawdust, and patients most commonly present with airborne contact dermatitis.

Lesions initially occur on the exposed areas of hands, forearms, face, and neck. Airborne sawdust, however, may drift inside clothing and adhere to axillae, waist, groin, and ankles (Le Coz and Ducombs 2006; Cabanillas et al. 2006; Podjasek et al. 2011). Irritation of oral, ocular, and respiratory mucosa may be present due to the spreading of the allergen by air.

Diagnosis

Tropical woods commonly contain quinones as main sensitizers. Occasionally, a precursor agent is present in the wood and must be oxidized to the quinone in the air or within the skin to produce sensitization (Podjasek et al. 2011).

Cross-reactivity between tropical woods occurs commonly because they contain similar allergenic substances. The wide presence of

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different quinones may explain the possible cross-reactions between woods belonging to different families (Le Coz and Ducombs 2006; Stingeni et al. 2008).

For example, 2,6-dimethoxy-1,4-benzoquinone is found in many woods, such as African or American mahogany (*Kaya* spp., Meliaceae family), bubinga (*Guibourtia* spp., Caesalpiniaceae family), capomo (*Brosimum alicastrum* Schwartz, Moraceae family), *Bowdichia* spp. (*Bowdichia nitida* Benth.) and *Diplotropis* spp. (*Diplotropis purpurea*), doussié (*Afzelia* spp.), Afrormosia or kokrodua (*Pericopsis elata* van Meeuwen), makoré (*Tieghemella Africana* Pierre, *T. heckelii* Pierre ex A. Chev.), sipo (*Entandrophragma* spp., Meliaceae family), wengé (*Millettia laurentii* De Wild, *Millettia stuhlmannii* Taub., Papilionaceae family), and Australian blackwood (*Acacia melanoxylon* R. Br., Mimosaceae family) (Le Coz and Ducombs 2006).

Dalbergiones such as (*R*)-3,4-dimethoxydalbergione, (*R*)- and (*S*)-4-methoxydalbergione, (*S*)-4,4-dimethoxydalbergione, and (*S*)-4-hydroxy-4-methoxydalbergione are sensitizers present in Brazilian rosewood or palisander (*Dalbergia nigra* All., Papilionaceae family); pau ferro, "santos palisander," or Caviuna vermelha (*Machaerium scleroxylon* Tul., Papilionaceae family); East Indian rosewood (*Dalbergia latifolia* Roxb.); cocobolo (*Dalbergia retusa* Helm., *Dalbergia granadillo* and *Dalbergia hypoleuca*); or grenadil (*Dalbergia melanoxylon* Guill. and Perr.) (Le Coz and Ducombs 2006).

Although major allergens in tropical woods are benzoquinones and naphthoquinones (Hausen 1986), the exact allergens in some wood families are still unknown (Kop et al. 2012).

Skin tests are needed to differentiate between allergic and irritant contact dermatitis. Wood dusts can be used for patch testing, but should not be tested as is, because there is a real risk of irritation and active sensitization. It is more advisable to dilute the dusts mixed in white petrolatum, 10–20 % (weight–weight). Extracts obtained with solvents such acetone or ethanol can also be used (Hausen 1986; Estlander et al. 2001; Le Coz and Ducombs 2006; Gómez-Muga et al. 2009).

If a specific commercial preparation of the known wood allergen is available, patch testing with it will better confirm the diagnosis.

It can be very difficult to distinguish between irritant and allergic patch test reactions to exotic wood. Patch test preparations must be checked for irritancy by test in controls, but it raises ethical consideration due to the risk of active sensitization.

Management

As with other contact allergies, avoidance of the allergen is an essential component of the treatment. However, allergen avoidance may be very difficult to perform. The use of barrier creams is usually not effective, and standard clothing is not good protection because the sawdust can be introduced into.

Adequate ventilation in the workplace, wearing protective clothing, and an excellent personal hygiene are useful measures of prevention.

Identification of the wood species is essential for diagnosis and appropriate advice to wood dust allergic people. Woods provide some difficulty with their identification. Especially the identification of imported woods may be troublesome, because they are transported under a trivial rather than botanical name, and often those trivial names are used incorrectly. The collaboration of an expert wood anatomist can help in identifying a sample of wood believed to be the cause of contact dermatitis.

The potential for cross-reactivity must be taken into account, and patients should be counseled to avoid woods with similar structured allergens.

Conclusion

Exotic woods induce contact dermatitis, mainly in woodworkers. Irritation is frequent, and contact allergy is due to potent allergens like quinones.

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Cross-References

- ▶ Contact Dermatitis Due to Plants
- ▶ Plants, Allergic Contact Dermatitis From

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Allergic Proctocolitis and Food Protein-Induced Enterocolitis Syndrome (FPIES)

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Synonyms

Allergic colitis (AC); Allergic proctocolitis; Dietary protein-induced enterocolitis syndrome (DPIES); Food protein-induced enterocolitis syndrome (FPIES); Food protein-induced proctitis/proctocolitis

Definition

Allergic proctocolitis is a non-IgE-mediated gastrointestinal disorder characterized by inflammatory changes in the rectum and distal sigmoid colon as a result of immune-mediated reactions to ingested foreign protein, most commonly found in breastmilk- or cow's milk- or soy-based formulas.

Food protein-induced enterocolitis, FPIES, is a non-IgE-mediated gastrointestinal disorder characterized by profuse, repetitive vomiting, often with diarrhea, that if untreated can lead to acute dehydration and shock as a result of immune-mediated reactions to ingested foreign protein.

Introduction

There are several pediatric gastrointestinal disorders which have been attributed to immunologic reactions to dietary proteins. Although it is difficult to classify food protein-induced gastrointestinal disorders under a single unifying concept, a consensus conference was held in 2000 that helped to clarify the clinical distinctions and underlying pathophysiology of each of

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these disorders. These immunologic reactions are now classified as IgE mediated, non-IgE mediated, or mixed (Sampson and Anderson 2000). The spectrum of non-IgE-mediated gastrointestinal disorders ranges from benign and self-limited proctocolitis to debilitating enteropathy (Caubet and Nowak-Wegrzyn 2011). These disorders generally are transient in nature, affect mostly infants, and target variable regions of the gastrointestinal tract with subsequent effects on the nutritional state of the patient. Allergic proctocolitis and food protein-induced enterocolitis are two of the most commonly recognized forms of non-IgE-mediated food hypersensitivity.

Allergic Proctocolitis

Background and Prevalence

Allergic proctocolitis/colitis is a condition characterized by inflammatory changes in the rectum and distal sigmoid colon as a result of immune-mediated reactions to ingested foreign protein (Odze et al. 1995). Symptoms typically begin within the first few weeks to months of life, but the exact prevalence is unknown. Some authors have suggested that only a small percentage of children (20 %) with colitis during infancy have allergic colitis whereas others have suggested that most, if not all, cases of colitis in the first year of life can be attributed to allergic colitis (Odze et al. 1995). In one series, with 22 infants with rectal bleeding, 14 or 64 % of the infants were diagnosed with allergic colitis by rectal biopsies, using $\geq$6 eosinophils per high-powered field as the diagnostic criteria (Xanthakos et al. 2005).

Clinical Manifestations

Allergic proctocolitis is found almost exclusively in infants in the first months of life who are either breastfed or fed standard cow's milk- or soy-based formulas (Lake et al. 1982). In a prospective study, Odze et al. found that the mean age of symptom onset was 66 days and that none of the infants were more than 10 months old at the time of symptom onset (Odze et al. 1995). These infants are generally healthy but pass blood-tinged stools and mucus. Parents typically report a gradual onset of bloody stools which increases in frequency unless the causal allergen is removed (Lake 2000). Children with proctocolitis may be fussy or have increased frequency of bowel movements, but rarely have diarrhea. They do not exhibit growth delay or poor weight gain (Lake et al. 1982).

Allergic proctocolitis commonly occurs in breastfed infants with milk- and soy-based formulas being the causative foods in the majority of remaining cases (Odze et al. 1995). In one prospective study, 95 breastfed infants who presented with blood-tinged stools were treated with sequential elimination of foods from the maternal diet. Sixty-five percent of infants were determined to have food-induced symptoms attributable to maternal ingestion of cow's milk, 19 % to egg, 6 % to corn, and 3 % to soy. The remaining infants improved only after weaning to an extensively hydrolyzed or amino acid-based formula (Lake 2000).

Diagnosis

The diagnosis is typically made based upon the clinical presentation and the resolution of symptoms with the elimination of the presumed causal allergen. Skin testing and in vitro immunoassays are not recommended as these tests evaluate for the presence of food-specific IgE and are therefore usually negative in allergic proctocolitis, which is not believed to be IgE mediated (Lake 2000). No single lab or biochemical test is either sensitive enough or specific enough to be diagnostic of allergic proctocolitis. However, the finding of either peripheral eosinophilia or eosinophilia in stool samples stained with Wright stain is suggestive of the disease (Odze et al. 1995).

Differential Diagnosis

The differential diagnosis for allergic proctocolitis includes necrotizing enterocolitis, anal fissure, infections, vascular malformation, intussusception, or a Meckel's diverticulum.

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Pathology

Knowledge of pathologic features of allergic proctocolitis is based primarily on information gained by endoscopy and the evaluation of mucosal biopsy specimens. Mucosal lesions are frequently confined to the rectum, although they may extend further up the colon (Lake et al. 1982). Mild colitis with patchy areas of erythema and loss of vascularity are the typical lesions seen. Increased nodularity suggestive of lymphoid hyperplasia has also been described (Odze et al. 1993). The most striking and characteristic histologic feature is the presence of focal infiltrates of eosinophils in all mucosal compartments, but particularly the lamina propria (Odze et al. 1993).

Management

In exclusively breastfed infants, continued breastfeeding should be encouraged if the mother is willing to eliminate the suspected food from her diet. Cow's milk should be eliminated first, in the absence of evidence implicating some other specific food (Lake et al. 1982). After implementation of an elimination diet, it may take up to 2 weeks for complete resolution of bloody stools; however, most cases improve within 72 h (Lake 2000). If the infant's symptoms fail to resolve, then soy, followed by egg, should also be removed from the mother's diet (Lake et al. 1982). For formula-fed infants, cow's milk- or soy-based formulas should be replaced with a protein hydrolysate formula. It is generally not recommended that an infant be changed from cow's milk to soy formula, as 10–30 % of children will be sensitive to both proteins (Powell 1978). It has been estimated that 5–10 % of infants with cow's milk- or soy-induced proctitis are intolerant of extensively hydrolyzed cow's milk formula. Therefore, infants who continue to bleed should be given an amino acid-based formula (Lake 2000).

Reintroduction of cow's milk- or soy-based protein formula can be done at home unless the infant initially presented with severe diarrhea and/or vomiting that would suggest concomitant enterocolitis or IgE-mediated hypersensitivity. For breastfed infants, similar parameters can be followed for the reintroduction of these proteins into the mother's diet (Lake 2000). Lake and colleagues suggest attempted reintroduction 4–6 months after the antigenic protein was eliminated. Before reintroduction of the inciting antigen, stools should be normal and tests for occult blood should be negative. If hematochezia or other symptoms of proctocolitis recur, it is recommended to resume the previous diet restrictions for an additional 5–6 months before rechallenge (Lake 2000).

After 6 months of age, 50 % of breastfed infants will tolerate the resumption of the offending protein; by 9 months of age, 95 % will tolerate resumption of the offending protein in the maternal diet or by formula. The prognosis is excellent and nearly all infants will be able to tolerate cow's milk and soy products by 1 year of age (Lake 2000).

Food Protein-Induced Enterocolitis Syndrome

Background and Prevalence

Food protein-induced enterocolitis syndrome (FPIES) is a potentially severe, non-IgE-mediated food protein hypersensitivity manifested by profuse, repetitive vomiting, often with diarrhea, that if untreated can lead to acute dehydration and shock (Caubet and Nowak-Wegrzyn 2011). The original description of food protein-induced enterocolitis syndrome likely dates back to 1967 when Dr. Gryboski of Yale published a case series of 21 children with what she termed "milk-induced colitis." In this series, symptoms were manifested primarily by diarrhea (n = 15/21), vomiting (n = 5/21), both vomiting and diarrhea (n = 1/21), and colic (n = 2/21). Their symptoms improved rapidly after the removal of bovine milk products from their diet and recurred with its introduction (Gryboski 1967). In 1978, Dr. Geraldine Powell published the first large study describing clinical features of food protein-induced enterocolitis syndrome patients. She also proposed four diagnostic criteria that are still used in clinical practice today as well as a standard challenge protocol (Powell 1978). Reports of a series of infants with food protein-induced enterocolitis by Sicherer et al. and Burks et al. further

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characterized clinical features and refined food challenge protocols (Sicherer et al. 1998 and Burks et al. 1994).

In a prospective, population-based study conducted in Israel, the incidence of FPIES was 3.4 per 1,000. All patients presented within the first year of life with recurrent vomiting (Katz et al. 2011). There is a slight male predilection in FPIES (52–60 %) (Katz et al. 2011; Mehr et al. 2009). Approximately 30 % of infants with FPIES develop atopic diseases. Family history of atopic diseases is present in 40–80 % of patients, including a family history of food allergy in approximately 20 % (Nowak-Wegrzyn and Muraro 2009).

Clinical Manifestations

Food protein-induced enterocolitis syndrome represents the severe end of the spectrum of non-IgE-mediated food protein-induced gastrointestinal diseases. FPIES manifests as profuse, repetitive vomiting and diarrhea in young infants, almost all of which are formula-fed. In the most severe cases, symptoms manifest within the first days of life with severe, bloody diarrhea, lethargy, abdominal distension, hypoactive bowel sounds, weight loss, failure to thrive, dehydration, metabolic acidosis and electrolyte abnormalities, anemia, elevated white blood cell count with eosinophilia and neutrophilia, and hypoalbuminemia (Nowak-Wegrzyn 2008). In 65 % of patients with a recorded white blood cell count, thrombocytosis (platelet count $>$ 500 x 10^9/L) was also seen (Mehr et al. 2009). Overall, 75 % of infants with FPIES appear acutely ill, including 15 % to 20 % with hypotension who require hospitalization and extensive evaluation before a diagnosis of FPIES is reached. In a study of 66 acute episodes in 35 children, emesis was present in 100 % of the episodes, lethargy in 85 %, pallor in 67 %, diarrhea in 24 %, and hypothermia (temperature $<$36 °C) in 24 % (Mehr et al. 2009). In infants with severe reactions and acidemia, methemoglobinemia has been reported; some infants have even required treatment with methylene blue and bicarbonate. These infants appear ashen-gray and listless (Nowak-Wegrzyn 2008). Intramural gas may be noted on abdominal radiographs, prompting a diagnosis of necrotizing enterocolitis, sepsis evaluation, and treatment with antibiotics. Ileus resulting in laparoscopy has also been reported (Nowak-Wegrzyn 2008).

Symptoms of FPIES may be chronic in nature while the antigen is being ingested on a regular basis, such as with cow's milk- or soy-based formula. In these cases, symptoms typically present in the first month of life with chronic diarrhea and intermittent vomiting, in association with failure to thrive and may progress to academia and shock. Later onset is associated with delayed introduction of milk or soy protein in breastfed infants (Leonard and Nowak-Wegrzyn 2011). This chronic initial phase can be followed by an acute phase if the antigen is removed from the diet for at least 2 to 3 days and subsequently reintroduced, with the above described classic symptoms starting approximately 1.5 to 2 h after ingestion (Powell 1978). Severe, repetitive vomiting generally occurs 1–3 h and diarrhea 5–8 h after feeding (Nowak-Wegrzyn and Muraro 2009).

The two most commonly implicated foods to trigger FPIES in the United States and Western European countries are cow's milk and soy. This contrasts slightly to a 16-year study conducted in Australia in which rice was the most common individual food trigger, followed by cow's milk and soy (Mehr et al. 2009). It had previously been thought that FPIES was not seen in exclusively breastfed infants; however, there was a case reported in 2011 by Monti et al. of an exclusively breastfed infant with clinical manifestations consistent with FPIES (Monti et al. 2011). Since that time, there have been several additional reports of FPIES in breastfed infants. FPIES may also be induced by solid food, such as rice, oats, barley, chicken, turkey, egg white, green pea, peanut, sweet potato, white potato, fruit protein, and fish and mollusks (Leonard and Nowak-Wegrzyn 2011). The mean age at onset with solid food FPIES is generally a bit later than that of cow's milk or soy FPIES, often presenting when these foods are first introduced between the ages of four and seven months (Mehr et al. 2009). Presumably, any food could cause FPIES. Rarely,

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the development of FPIES can be seen after 1 year of age, often when the inciting food is fish or shellfish (Sampson and Anderson 2000). Published studies regarding cross-reactivity between milk and soy have been conflicting. Some report cross-reactivity rates greater than 50 %, whereas other studies did not see any cross-reactivity between milk and soy (Burks et al. 1994; Mehr et al. 2009). Similar controversy exists regarding whether children with FPIES to rice are at increased risk of FPIES to other grains. There have been individual case reports of FPIES caused by both rice and wheat as well as FPIES caused by both rice and oat. Wheat, rye, and barley are closely related and are more genetically distant from rice and oat. Therefore, when concern for potential cross-reactivity exists, one could attempt to introduce one of these more distantly related cereals (Mehr et al. 2009). Among infants with solid food FPIES, 80 % reacted to more than one food, 65 % were previously diagnosed as having cow's milk and/or soy FPIES, and 35 % were breast-fed (Nowak-Wegrzyn et al. 2003).

Diagnosis

The diagnosis of food protein-induced enterocolitis relies on history, clinical features established by Powell in 1978, exclusion of other etiologies, and an oral food challenge. Powell proposed the following clinical criteria: (1) age less than 9 months at initial diagnosis; (2) repetitive vomiting, diarrhea, or both within 24 h of ingestion; (3) lack of other symptoms related to the offending food; and (4) resolution of symptoms after the removal of the food from the diet (Powell 1978). Although an oral food challenge is the gold standard for diagnosing FPIES, most infants do not require confirmatory challenges for initial diagnosis. Oral food challenges in this population are considered particularly high risk, as approximately 50 % of the reactive challenges will require intravenous fluid replacement (Caubet and Nowak-Wegrzyn 2011). Oral food challenges remain necessary if the history is unclear and to determine whether FPIES has resolved before a food is reintroduced into the diet (Nowak-Wegrzyn 2008).

Unfortunately, there are no reliable laboratory tests to aid in the diagnosis of FPIES. More than 90 % of patients have negative skin prick test results and undetectable food-specific IgE at diagnosis. When food-specific IgE is detected, the course of FPIES tends to be more protracted, and the potential for developing symptoms of IgE-mediated allergy is increased (Sicherer et al. 1998). The utility of atopy patch testing (APT) was evaluated in 19 infants aged 5 to 30 months with challenge-confirmed FPIES. APT predicted 28 of 33 outcomes of oral food challenges. The negative predictive value in this study was 100 %, and the positive predictive value was 75 % (Fogg et al. 2006). These findings have not been repeated; therefore, at this time, atopy patch testing is not part of the standard workup of FPIES.

Given the absence of cutaneous or respiratory symptoms, the delay in the onset of symptoms from the time of food ingestion, and the ill appearance of many children at the time of presentation, FPIES cases are often misdiagnosed as sepsis, a metabolic disorder, anaphylaxis, or a surgical abdomen. Misdiagnosis leads to additional, often painful, investigations and prolonged hospital admissions.

Differential Diagnosis

The differential diagnosis for food protein-induced enterocolitis syndrome includes other non-IgE-mediated gastrointestinal food hypersensitivities, namely, allergic proctocolitis and food protein-induced enteropathy, IgE-mediated anaphylaxis, necrotizing enterocolitis, sepsis, metabolic disorders, gastrointestinal infections, Hirschsprung's disease, intussusception, and volvulus.

Pathology

There are no studies in which endoscopic biopsies are performed solely in patients with food protein-induced enterocolitis syndrome since the diagnosis of FPIES is based on clinical criteria. However, several case series include patients who fulfill criteria for the diagnosis of FPIES and describe varied gross and histologic features. Endoscopic evaluation reveals diffuse colitis with variable ileal involvement. In the most severe cases, focal erosive esophagitis and

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gastritis are found with prominent eosinophilia and villous atrophy (Fontaine and Navarro 1975). Colonic mucosa may demonstrate mild friability to spontaneous hemorrhage and ulcerations similar to those seen in ulcerative colitis. Crypt abscesses have been identified in some patients (Nowak-Wegrzyn 2008). Jejunal biopsies reveal flattened villi, edema and increased numbers of lymphocytes, IgM- and IgA-containing plasma cells, eosinophils, and mast cells. Rectal ulceration and bleeding with friability of the mucosa has been seen in cases of FPIES (Fontaine and Navarro 1975).

Proposed Pathophysiology

It has been hypothesized that ingestion of food allergens causes local inflammation leading to increased intestinal permeability and fluid shift, which ultimately results in the clinical symptoms seen in FPIES, namely, emesis, diarrhea, dehydration, and lethargy. However, one study showed that baseline antigen absorption is normal and does not predispose patients to FPIES (Powell et al. 1989). The inflammatory responses induced by the food allergen in FPIES are thought to involve a number of different cell types as highlighted below.

FPIES is often considered a T-cell-mediated disorder; however, the role of T cells has not been clearly elucidated. Heyman et al. postulated a T-cell-mediated response in which proinflammatory cytokine TNF-α release would alter intestinal permeability. Their results indicate that the high level of TNF-α released by antigen-specific T cells acts synergistically with IFN-γ to increase intestinal permeability. This may contribute to the influx of antigens into the submucosa with further activation of antigen-specific T cells (Heyman et al. 1994). A critical role for TNF-α was further supported by the findings of increased amounts of fecal TNF-α in patients with cow's milk-induced gastrointestinal reactions (Caubet and Nowak-Wegrzyn 2011). Chung et al. examined the presence of TNF-α in duodenal biopsy specimens by immunostaining. They recorded a higher staining for TNF-α in infants with FPIES and with villous atrophy compared with those without villous atrophy and with the control group (Chung et al. 2002). Taken together, these data support a major role of TNF-α in the acute and chronic symptoms of FPIES. The regulatory cytokine TGF-β1 is known to induce T-cell suppression and acts to protect the epithelial barrier of the gut from the penetration of foreign antigen. It is also known to stimulate the synthesis of extracellular matrix proteins, collagen, and fibronectin and enhance the binding between cells and matrix proteins by altering the expression of integrins. A decreased expression of TGF-β1 has been described at the level of the intestinal mucosa in infants younger than 3 months of age. Chung et al. demonstrated that the type 1 receptor for TGF-β was decreased in duodenal biopsy specimens in FPIES patients compared with controls. These results suggest that the impaired function of the epithelial barrier caused by the decreased TGF-β receptor 1 activity may contribute to the pathogenesis of FPIES (Chung et al. 2002). The overall imbalance in TGF-β/TNF-α may be important in the pathophysiology of FPIES.

Leukocytosis with a left shift has long been recognized as a common finding for patients presenting with acute FPIES and was included in the original diagnostic criteria proposed by Powell. In the Powell study, peripheral blood neutrophil counts were elevated in all positive challenges, peaking at 6 h with a mean increase of 9,900 cells/μL (Powell 1978). Similar findings have been found in other studies. Neutrophils have also been found in stool mucus of FPIES patients. The increase in peripheral neutrophils most likely occurs as a result of the secretion of different cytokines and chemokines during the inflammatory reaction, in which TNF-α may play a role (Mehr et al. 2009).

Humoral immune responses in FPIES are generally not considered to be an important part of the pathogenesis of the disease. An increase in serum food antigen-specific IgA and IgG antibody levels has been noted in FPIES patients in one study. Another group found lower levels of serum cow's milk-specific IgG4 antibody levels and a trend for higher IgA antibody levels in patients with cow's milk FPIES when compared to a control group (Caubet and Nowak-Wegrzyn 2011).

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The role of IgG and IgA antibodies in the pathogenesis of FPIES needs further exploration.

Management

Management of FPIES consists of removing the offending food from the diet. For infants, exclusively breast-feeding can be protective. If this is not possible or the infant is exclusively formula-fed, casein hydrolysate-based formula is recommended due to frequent concomitant cow's milk and soy FPIES. In some cases, amino acid formula is needed. As previously discussed, approximately one-third of infants with cow's milk or soy FPIES develop solid food FPIES. Since reactions to rice and grains represent the most common types of solid food FPIES, it has been suggested that yellow fruits and vegetables instead of cereal be introduced at 6 months of age in these patients (Nowak-Wegrzyn et al. 2003). Because of the high rate of reaction to multiple foods, it may benefit infants with solid food FPIES to avoid grains, legumes, and poultry during the first year of life (Sicherer 2005). Introduction of cow's milk and soy in infants with solid food FPIES may be attempted after 1 year of age if there is no prior history of reactivity to these foods. Tolerance to one food from each high-risk group (i.e., oat from grains) increases the likelihood of tolerance to other foods in the same group (Sicherer 2005).

Oral food challenges can be used to evaluate the possibility that FPIES has been "outgrown" in an individual patient (Nowak-Wegrzyn 2008). There is no clear consensus at this time as to when follow-up challenges should be performed. Some advocate performing challenges every 18 to 24 months in patients without recent reactions (Sicherer 2005). However, in a Korean study which included 27 infants with cow's milk FPIES, 64 % tolerated cow's milk at 10 months and 92 % tolerated soy at 10 months. These investigators therefore recommend follow-up challenges at 12 months of age for cow's milk and between 6 and 8 months of age for soy (Hwang et al. 2009).

Oral food challenges involve the administration of food protein, 0.06–0.6 g/kg body weight, with lower doses used in children with a history of severe reactions (Nowak-Wegrzyn 2008). Generally, the amount of protein served initially during an oral food challenge should not exceed 3–6 g of food protein. The calculated amount of food is divided into three equal portions and served over 45 min. The patient is observed for 2–4 h, and if asymptomatic, a second feeding, often an age-appropriate regular serving amount, is given followed by observation for several more hours (Sicherer 2005). It should be noted that oral food challenges in FPIES patients are a high-risk procedure and should only be conducted under physician supervision. Given the risk for severe dehydration and/or shock, an IV should generally be placed prior to the initiation of the challenge. Intravenous hydration is first line therapy for acute symptoms during a challenge; however, corticosteroids are often used as well for severe reactions based on the presumed pathophysiology that involves T-cell-mediated intestinal inflammation. Epinephrine should be available for severe cardiovascular reactions or shock; however, the efficacy of epinephrine has not been established in FPIES. In one group's experience, the prompt administration of epinephrine did not improve the symptoms of emesis and lethargy, which instead resolved promptly with IVF administration (Nowak-Wegrzyn 2008).

Challenge results are considered positive if the following symptoms are present: emesis (onset, 1–3 h), lethargy (onset, 1–3 h), and diarrhea (onset, 2–10 h; mean 5 h). Laboratory findings seen with positive challenges include elevated neutrophil count (>3,500/μL) and fecal leukocytes (Powell 1978).

Resolution of FPIES appears to be somewhat population dependent, especially for cow's milk and soy FPIES. In one large US referral center, cow's milk FPIES resolved in approximately 60 % by 3 years of age. In contrast, a Korean cohort showed more than 60 % resolution by 10 months of age, and in an Israeli cohort, there was 90 % resolution by 3 years of age (Katz et al. 2011; Nowak-Wegrzyn et al. 2003; Hwang et al. 2009). In soy FPIES, only 25 % of cases resolved by 3 years of age in the US cohort in contrast to more than 90 % resolution by 10 months of age in the Korean cohort (Nowak-Wegrzyn et al. 2003;

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Hwang et al. 2009). This difference may be explained by a higher percentage of patients in the US cohort with detectable levels of food-specific IgE, representing cases of atypical FPIES. Resolution of solid food FPIES has not been as extensively studied. In the US cohort, resolution by 3 years of age occurred in 67 % for vegetables, 66 % for oat, and 40 % for rice (Nowak-Wegrzyn et al. 2003).

Conclusion

Allergic proctocolitis and food protein-induced enterocolitis syndrome represent non-IgE-mediated food hypersensitivity gastrointestinal disorders. Both entities are typically present in the first year of life, and the majority of cases resolve by 3 years of age. The mainstay of treatment is avoidance of the suspected antigen from the diet. As more insight into the pathophysiology of these disorders is gained, noninvasive diagnostic tests may become available, aiding in diagnosis and monitoring of disease progression. Heightened awareness and increased attention should also lead to early, accurate diagnosis and management.

Cross-References

- ▶ Cow's Milk Allergy
- ▶ Diagnostic Components: Allergen for In Vivo (Skin Testing, Immunotherapy) and In Vitro (Serology) IgE Antibody Testing
- ▶ Diagnostic Food Challenges
- ▶ Fatal Allergic Reactions to Foods
- ▶ Food Allergens
- ▶ Food Allergies, Diagnostic Testing
- ▶ Food Allergy, Overview
- ▶ Nutrition in Food Allergy
- ▶ Specific IgE

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Aluminum Allergy

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Synonyms

Aluminum contact dermatitis; Delayed aluminum hypersensitivity

Definition

Aluminum contact allergy is defined as an inflammatory process caused by contact with exogenous aluminum.

Introduction

Aluminum is the most abundant metal in the Earth's crust and the third most abundant of all elements (after oxygen and silicon). Almost all metallic aluminum is produced from bauxite. Despite its natural abundance, aluminum has no known function in biology. It is remarkably nontoxic but some toxicity can be traced to deposition in bone and the central nervous system.

Uses

Aluminum compounds are widely used. It is present in drinking water, especially in urban areas, as well as in food such as soy-based milk products, baking powder, frozen products, and many more. Many food additives such as preservatives, coloring, leavening, and anticaking agents are intentionally mixed with aluminum. Furthermore, aluminum is used in water purification, sugar refining, and brewing. Many drugs use aluminum (antacids, analgesics, antidiabetic drugs, etc.). Depending on those variables, ingestion of aluminum in humans can vary greatly between countries from 2 to 160 mg/person/day. The most important cutaneous routes of aluminum exposure are vaccination with aluminum-containing vaccines, allergen-specific immunotherapy with aluminum-absorbed extracts, and contact with aluminum in antiperspirants and other skin care products.

Another environmental aluminum exposure is the extensive use of antiperspirant products and toothpaste containing aluminum, but there are only few reports in literature (Williams and Freemont 1984; Veien et al. 1993). One study described a granulomatous reaction in a tattoo caused by aluminum (McFadden et al. 1989).

Prevalence and Clinical Picture

Aluminum, both in its elemental and in its salt forms, has been regarded to be a weak allergen, and contact allergy to aluminum is thought to be rare, despite the extent of environmental exposure (Davis et al. 2011).

Most reported cases of delayed hypersensitivity to aluminum and development of persistent itching nodules at the injection site have occurred following deposition in the dermis or subcutis of

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vaccines used for childhood immunizations or after allergen-specific immunotherapy (SIT) with antigen extracts absorbed to aluminum.

Contact allergy to aluminum was demonstrated in 77 % of 645 children with itching nodules after vaccination with aluminum hydroxide-adsorbed cellular monocomponent pertussis vaccine, combined diphtheria-tetanus-acellular pertussis vaccine, and diphtheria-tetanus toxoid vaccine in Denmark (Bergfors et al. 2008). An additional 19 cases of aluminum contact allergy and persistent pruritic nodules after injection of commonly used aluminum-adsorbed vaccines in Sweden have been reported (Bergfors et al. 2005).

A cross-sectional study on children who had undergone SIT at a pediatric unit in Sweden reported contact allergy to aluminum in 8/37 patients (Netterlid et al. 2009). Six of those eight patients had persistent itching nodules. In a control group of patients not exposed to SIT, no cases of aluminum allergy were detected, reaching the conclusion that there was probably an association between contact allergy to aluminum and persistent subcutaneous nodules. The same group aimed to quantify this possible association in a recent study by patch testing and using questionnaires in children and adults entering an allergen-specific immunotherapy randomized, controlled, single-blind multicenter study (Netterlid et al. 2013). A total of 205 individuals (78 children and 127 adults) completed the study. Contact allergy to aluminum was found in eight participants (3.9 %), four in the exposed groups after 1 year of treatment of SIT and four in the unexposed group, overrepresented in young individuals and in those with atopic dermatitis, showing that the result does not necessarily imply that SIT is a risk factor for the induction of contact allergy to aluminum.

Aluminum Allergy, Fig. 1 False multiple sensitizations due to aluminum allergy in patch tests (By courtesy of G. Perdomo)

Diagnosis

There have been different aluminum compounds which have been used in patch testing to demonstrate contact allergy to aluminum. Initially, aluminum chloride hexahydrate in petrolatum at 2 % and an empty test chamber (Finn Camber®, ○ = 8 mm; Epithets Ltd Oyo, Tuzla, Finland) made of elemental aluminum were used for patch testing. More recently, a higher test concentration of aluminum chloride hexahydrate at 10 % in petrolatum was suggested as the preparation of choice for the diagnosis of contact allergy to aluminum (Bruze et al. 2008). In a recent study investigating different aluminum test preparations regarding an optimal compound and an optimal test concentration, interestingly, the highest number of positive reactions was not noted to aluminum chloride hexahydrate at 20 %, but to the lower concentration of 10 %, similar to findings in previous surveys. In this study, another aluminum salt, aluminum lactate, not used previously in patch testing but an ingredient found in toothpaste and antiperspirants, showed a similar pattern of elicitation as aluminum chloride hexahydrate (Siemund et al. 2012).

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Positive reactions to aluminum compounds apparently are difficult to reproduce. Seventy-seven percent of the children (186/241) with demonstrated aluminum allergy were retested after 5–9 years and did not show any reaction to aluminum chloride hexahydrate at 2 % in a -Swedish study (Gente Lidholm et al. 2013). A similar interesting observation was described by Netterlid et al. in 5 of 8 patients (63 %), in which the aluminum allergy could not be verified with the same test concentration as used before (Netterlid et al. 2013). This phenomenon may indicate that aluminum reactivity decreases over time or an individual variation in aluminum reactivity as has been shown for nickel contact allergy (Hindsén et al. 1999).

If there is suspicion of allergy to aluminum, it is important to avoid aluminum test chambers in the making of patch testing and to use plastic chambers as an alternative. When patch tests made with aluminum test chambers show multiple positivities, it is important to rule out an aluminum allergy (Fig. 1).

Conclusions

Despite its natural abundance and considering the extent of use, aluminum is regarded as a weak allergen, and contact allergy to aluminum is thought to be rare.

Most reported cases of delayed aluminum hypersensitivity have been related to deposition in the dermis or subcutis of vaccines used for childhood immunizations or following specific allergen immunotherapy, but so far, this does not necessarily imply to be a risk factor for the induction of contact allergy to aluminum. Pruritic, deep nodules at injection site are characteristic.

Aluminum chloride hexahydrate at 10 % in pet. gives the highest number of positive aluminum reactions. Patch testing with aluminum chloride hexahydrate at 2 % in pet. or an empty Finn Chamber® and the intradermal test with the salt are insufficient methods to demonstrate contact allergy to aluminum. Positive reactions to aluminum compounds apparently are difficult to reproduce.

Cross-References

- ▶ Contact Dermatitis Due to New Metals
- ▶ Safety of Immunotherapy

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Analytes and Biomarkers: Environmental Allergen Assessment

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Synonyms

Cat (Fel d 1); Dog (Can f 1); Dust mite (Der p 1, Der p 2, Der f 1, Der f 2); German cockroach (Bla g 1); Mold spore analysis; Mouse (Mus m 1); Rat (Rat n 1)

Definition

Environmental allergen quantification involves the combination of environmental sampling and laboratory analyses to detect and quantify the level of indicator allergenic components for the principal allergen specificities in indoor surface reservoir dust that trigger ocular, nasal, and respiratory allergic symptoms in sensitized individuals.

Introduction

Of the four modalities of allergic disease management, allergen avoidance is possibly the most effective and least expensive approach. Other strategies such as pharmacotherapy (e.g., antihistamines), immunotherapy (allergen injections), and anti-IgE therapy are often used together with avoidance to manage an allergic individual's symptoms. Since it is not possible to control outdoor aeroallergen exposure except by wearing protective devices (e.g., masks, gloves), environmental allergen quantitation principally involves the confirmation of an allergen source in an indoor environment. The first step, before any environmental testing is performed, is to verify that the symptomatic individual living in the environment in question has IgE antibody-induced sensitivity to one or several known indoor allergens (Hamilton 2010). Once the person is known to be allergic to an indoor aeroallergen, only then are they candidates for an evaluation of their environment for allergen content.

Identification of Allergens

An allergen is a natural environmental substance that is generally innocuous to most people. However, when a genetically predisposed individual encounters the allergen, they generate specific IgE antibodies which bind onto mast cell and basophil high-affinity IgE receptors. Following reexposure of the subject to the allergen, preformed specific IgE antibodies bind to the new source of allergen and activate these cells, resulting in the release of inflammatory mediators that produce allergic symptoms.

The identification of clinically important allergens begins by evaluation of the clinical histories of a group of affected individuals. Allergic symptoms need to be temporally related to a known allergen exposure, even though the actual magnitude and type of symptoms may vary with the allergen specificity, dose, and route of exposure. Following an association between an observed allergic symptom and an objectively defined allergen exposure, a blood specimen is collected from symptomatic individuals, and allergen-specific IgE is detected to verify sensitization to a particular allergen specificity. The overall clinical importance of a given allergen within a population of allergic patients is defined by the percentage of individuals who produce IgE antibody which specifically binds the allergenic molecule. A "major" allergen is one in which over 50 % of individuals experience symptoms to a given allergen and produce an IgE antibody specific for the allergenic molecule. Feline ureteroglobulin (*Felis domesticus* group 1 allergen or Fel d 1) is a good example of a major allergen that is present in cat dander. From 60 to 90 % of cat-allergic patients produce IgE antibody specific for Fel d 1. Once major

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allergens were identified for the principal indoor allergen groups (dust mites, pet epidermals, insects, rodents, mold), they became "indicator allergens" which when quantified, helped identify an environment that places a sensitized individual at risk for allergic symptoms following subsequent allergen exposure.

Indoor Aeroallergen Sources

Upper and lower airway allergic symptoms are readily induced in indoor environments by elevated levels of allergenic molecules released by dust mites, fur-bearing pets and rodents, insects (e.g., cockroaches and Asian lady bugs), and molds (Hamilton 2005). For each of the indoor aeroallergen specificities, a major allergenic molecule is used to indicate an environment as having a low, moderate, or high level of that allergen. The quantified level of each indicator allergen can be then used to identify an environment that places a sensitized and symptomatic individual living in that environment at risk for upper and/or lower airway allergic symptoms (Hamilton and Eggleston 1997). In addition, the allergen exposure risk to inhabitants can be influenced by other factors including the structure of the building, type of heating and cooling systems, the season, temperature and humidity, number of pets in and around the building, the number of residents, and the type of furniture and flooring (carpets vs. hard wood or tiled floors).

Dust Mites

Four species of arachnid mites commonly populate homes: *Dermatophagoides* (D.) *pteronyssinus*, *D. farinae*, *D. microceras*, and *Euroglyphus maynei* (Spieksma and Dieges 2004). They live and breed in mattresses, carpets, and upholstered furniture, where they consume skin and dander shed from humans and animals and they absorb water from the air. Dust mites produce ~200 times their body weight in fecal pellets during their 2–3.5-month life span. Furthermore, they deposit body parts into household dust as they die. Their heavy fecal pellets and decaying body parts release potent allergens into surface reservoir dust that include among other proteins the group 1 and 2 allergens from *D. pteronyssinus* (Der p 1 and 2) and *D. farinae* (Der f 1 and Der f 2) (Thomas et al. 2004). Der p 1, Der f 1, Der p 2, and Der f 2 are currently used as indicator allergens in reservoir to identify high levels of dust mites in an indoor environment.

Fur-Bearing Animals

Many domesticated animals including cats, dogs, guinea pigs, hamsters, rabbits, rats, and mice produce dander, saliva, and urine that contain potent allergens. The domestic cat (*Felis domesticus*) produces a potent allergen (Fel d 1) in its sublingual mucous salivary glands and hair root sebaceous glands that tenaciously attaches to respirable dust particles (2–10 μm in size) and fibers on upholstered surfaces (carpets and upholstered furniture) (Leitermann and Ohman 1984). Levels of Fel d 1 allergen can be used to indicate the burden of cat allergen in an indoor environment. Fel d 1 can be transported into an area on the clothing of people who have household pets, and thus even pet-free homes and classroom environments can have low levels of cat allergens (Bollinger et al. 1996). Allergenic proteins are also released in the hair and dander of the domesticated dog (*Canis familiaris*) (de Groot et al. 1991). Can f 1 is the principal dog allergen that is an indicator for dog allergen burden in house dust.

Rodents and Pests

Mice and rats are among the rodents which produce clinically important allergens. Mus m 1 and Rat n 1 are used as the indicator allergens for the detection of these allergens in reservoir dust specimens from homes (Matsui et al. 2005). Since most other pets are kept outdoors, dander from horses, cows, ducks, geese, and goats represent an insignificant risk for indoor allergen exposures, and thus, their allergenic burden in homes is not currently assessed by laboratory assays. Cockroaches produce highly potent allergens from their saliva, fecal material, secretions,

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cast skins, and dead bodies that can trigger asthma symptoms in sensitized children when exposed in indoor environments (Arbes et al. 2004). Of the 50 varieties of cockroach, the German cockroach (*Blattella germanica*) and the American cockroach (*Periplaneta americana*) represent the principal concern for most home owners. Bla g 1 and 2 are indicator allergens that are used to identify a cockroach allergen exposure risk in homes. When sampling for cockroach allergen, one needs to collect reservoir dust from the dining room, kitchen, and additional areas of the home where food is consumed and stored.

Indoor Aeroallergen Analysis

Prior to any sampling, the symptomatic individual needs to be evaluated to document their allergen sensitivities by skin testing or serology. The indoor environment in question also needs to be assessed for obvious sources of allergen contamination such as the presence of a pet (cat or dog) in the house or next door, mouse or rat droppings, dead cockroaches, or a musty odor with visual signs of water damage and mold growth. Obvious issues identify the need for remediation without the need for a formal aeroallergen analysis (Sheehan et al. 2010).

Homes are considered the principal location where aeroallergen sampling is performed. Schools and workplaces are less problematic since they are generally well maintained and they use less upholstered furniture and carpets. The exception is the early learning or day care center where stuffed toys, bedding, carpeting, and upholstered furniture are often extensively used (Perry et al. 2008).

A dust sample is collected from principal living areas by the homeowner using a commercially available kit. Dust collectors attach to the end of a standard household vacuum and are made of materials that trap particles in the respirable range down to 1 μm in size. Once sent to the laboratory, the specimen is processed by sieving through a wire mesh that passes 250 μm particles and removes large debris such as insect parts, hair, food particles, synthetic fibers, and lost coins and pins. The fine dust is then extracted in a physiological buffer containing an irrelevant protein to prevent loss during extraction. Following centrifugation to sediment large particulate, the specimen is sterile filtered and analyzed in a monoclonal antibody-based enzyme immunoassay for quantification of the relevant indicator allergens (Luczynska et al. 1989; Earle et al. 2007). Dust mite (Der p 1 and 2, Der f 1 and 2), cat (Fel d 1), dog (Can f 1), cockroach (Bla g 1 and 2), mouse (Mus m 1), and rat (Rat n 1) allergen levels are reported in mass units per ml of extraction buffer. Laboratories may participate in interlaboratory proficiency programs to insure consistency in results over time (Pate et al. 2005).

The lower the overall level of allergen in the environment, the lower the risk for allergic symptoms in an individual who is sensitized to that allergen. For dust mite allergens, levels >2,000 μg/g of surface reservoir dust of Der p 1, Der p 2, Der f 1, or Der f 2 were associated with increased risk of sensitization, and levels >10,000 μg were associated with an increased risk of allergic symptoms (Platts-Mills et al. 1990, 1991). For cat and dog allergens, Fel d 1 and Can f 1 allergen levels >8,000 and >80,000 ng/g of fine dust in an environment are levels above which there is an increased risk for allergic sensitization and symptoms, respectively. Since no target levels have been identified for indicator allergens of mouse, rat, or cockroach, any detectable level of these indicator allergens is considered indicative of a home that places a sensitized individual at risk for allergic symptoms (Hamilton et al. 1992).

Indoor Mold

In contrast to the other indoor aeroallergens, the number of viable mold spores or colony-forming units in a dust specimen may be most useful measurement in making decisions about remediation. Mold assessment can be particularly

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useful after water damage has occurred that produces prolonged high humidity. Indoor mold concerns when identified by a musty order or visual evidence of surface discoloration on the floor, walls, windows, or ventilation system preclude the need for laboratory testing. Since mold spores survive on many different surfaces (wood, paper, carpet, soil, plants, fabrics), sampling and testing are a challenge. Samples can be obtained as (a) a bulk "reservoir" dust from the floor or ventilation system, (b) sampling of a piece of the physical surface that is discolored, (c) performing a residual surface swipe on a suspected contaminated surface, and (d) obtaining an air sample using a multistage sampler that is equipped with a nutrient-filled culture plate.

Importantly, since there are no federal limits for acceptable levels of mold spores in an indoor environment, mold spore confirmation testing does not provide definitive information for making decisions about remediation. Once the specimen is collected, it can be analyzed by tissue culture, microscopic evaluation, DNA analysis, and immunoassay for indicator allergen content. For bulk dust specimens, a microbiologic assay can be readily performed to quantify the number of viable mold spores. This involves distributing sieved fine dust from the bulk specimen in a physiologic buffer onto growth medium in a culture plate that contains antibiotics to prevent bacterial growth. If present, mold spores grow into colonies that are visually enumerated at 24, 48, or 72 h. Normative data are available on the number of viable colonies per gram of surface dust in homes across the United States (Wood et al. 1988; Hamilton 2005).

There are also monoclonal antibody-based immunoassays available to quantify indicator allergens for *Aspergillus fumigatus* (Asp f group 1 [ribotoxin]) and *Alternaria alternata* (Alt a group 1 allergen [acidic glycoprotein]). However, a serious limitation resides as stringent nutrient requirements are not always optimal for efficient growth of *Aspergillus fumigatus* or *Alternaria alternata* and expression of these allergenic proteins.

Summary

Environmental allergen analysis begins by documenting sensitization in the patient and performing a careful visual review of the indoor environment for obvious signs of allergenic sources that can create exposure risks. Once the individual is known to be sensitized (IgE antibody positive) to dust mite, cat, dog, cockroach, mouse, rat, or mold allergen, a systematic evaluation of the indoor environment can be performed. This often involves collection of a reservoir dust specimen using a commercial collector connected to a household vacuum. The specimen is then sent to a specialized laboratory where it is processed (sieved, extracted, filtered) and analyzed by monoclonal antibody-based enzyme immunoassays for allergen content. The levels of allergen can then be used to make decisions about the health risks that the environment poses to the sensitized dweller and whether costly remediation is appropriate.

Cross-References

- ▶ Allergen Avoidance: Avoidance Strategies for Skin Allergies
- ▶ Allergen Avoidance: Cockroach and Rodent Avoidance
- ▶ Allergen Avoidance: Dust Mite Avoidance
- ▶ Allergen Avoidance: Fungi and Mold Avoidance
- ▶ Allergen Avoidance: Furry Animal Avoidance
- ▶ Specific IgE

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Analytes and Biomarkers: IgE

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Synonyms

Immunoglobulin E; Reagin

Definition

IgE – human IgE is an immunoglobulin of the approximate molecular weight of 190,000, which exists normally in monomeric form and constitutes approximately 0.0005 % of the total serum immunoglobulins. It binds with high affinity to FcεR1 receptors mainly expressed on mast cells and basophils and FcεRII receptors on a number of other cells. IgE mediates the production and release of vasoactive mediators following the binding of allergen and is the gatekeeper of immediate-type hypersensitivity reactions in allergic disease.

Introduction

IgE was identified in 1967 as a unique human immunoglobulin class or isotype (Ishizaka and Ishizaka 1967; Bennich et al. 1968; Johansson 2005; Hamilton 2005; Kirpatrick 2005). Structurally, IgE molecules contain two light chains (kappa, lambda) and two heavy (epsilon) chains. Each heavy chain contains five structural domains (VH, Ce1, Ce2, Ce3, and Ce4) that possess its unique antigenic and structural attributes that confer its special biological properties. IgE has a reported molecular weight of 190,000 Da.

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Total IgE

The circulating levels of IgE in blood are age dependent and at the lowest of any of the five human immunoglobulin isotypes (0–0.00004 g/L). The total serum IgE level in cord blood is usually <2 kU/L (<4.8 ug/L) due to the fact that IgE does not readily cross the placental barrier. Healthy children experience a progressive increase in their serum IgE levels up to the age of 10–15 years. Half of the IgE is distributed into the extravascular space. IgE has a relatively high fractional catabolic rate which is partly due to its removal from the plasma into tissue. While IgE does not pass the placenta or activate the classical complement pathway, its reaginic (mast cell sensitizing) activity is dependent on its ability to bind to the alpha chain of the high-affinity IgE Fc-epsilon receptor (FcεRI), which resides on the membrane surface of basophils and tissue mast cells.

Total serum IgE reference intervals from an age-stratified, healthy, skin test-negative (non-atopic) population are used to judge the relative level of total serum IgE in the serum of a patient (Barbee et al. 1981). Abnormally elevated IgE levels are associated with atopic disorders such as allergic rhinitis, extrinsic asthma, and atopic dermatitis. Excessive elevations in the serum IgE concentration are observed in parasite infections and are necessary for the diagnosis of the hyper-IgE syndrome. Low total serum IgE levels support the diagnosis of nonallergic asthma and help to exclude bronchopulmonary aspergillosis.

Free IgE

In 2003, Omalizumab (Xolair) was licensed for use in the management of severe asthma, especially in children who are not effectively managed by other therapeutic strategies (Busse et al. 2001; Lin et al. 2004). Omalizumab is a therapeutically administered humanized IgG1 antihuman IgE Fc that binds to an epitope on the epsilon heavy chain, which itself binds to the alpha chain of the high-affinity IgE receptor (α-FcεR1). By administering omalizumab, one can block the binding of "Free" or unbound IgE to FcεR1. Thus, Free IgE is IgE that circulates in blood in an unbound state, free of attachment to therapeutically administered humanized IgG anti-IgE, soluble IgE receptors, or other binding factors. Omalizumab administration also downregulates the number of FcεR1s on the surface of mast cells and basophils. The overall consequence is an observed reduction of allergic symptoms experienced by most individuals following allergen exposure. A total serum IgE levels between 30 and 700 IU/mL is required based on manufacturer recommendations to be a candidate for Omalizumab therapy. A pre-dosing total serum IgE measurement is required to determine the proper dose for optimal treatment efficacy (Busse et al. 2001; Holgate et al. 2004). Free IgE levels have been monitored using research assays that employ a biotin-labeled or biotin-insolubilized form of α-FcεR1 (Hamilton et al. 2005).

Allergen-Specific IgE

In contrast to total serum IgE, the presence of allergen-specific IgE antibody on basophils or skin mast cells or in the serum is highly predictive of an individual's propensity to exhibit an allergic response upon reexposure to the allergen. Before its identification in 1967, only in vivo bioassays (skin test, bronchial, or nasal provocation tests) were available to detect IgE antibody. The radioallergosorbent test or RAST was the first in vitro assay which could detect allergen-specific IgE antibody in serum (Wide et al. 1967). Today, three autoanalyzer-based assays (Hamilton 2010), a lateral flow assay (Sarratud et al. 2010), and a chip-based microarray (Jahn-Schmid et al. 2003) that are based on the same solid phase immunoassay design are available for detection and quantification of allergen-specific IgE. These methods differ in their relative analytical sensitivity and in the actual reported levels of allergen-specific IgE that are measured in human serum, especially

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following the administration of Omalizumab (Hamilton 2006, 2010).

The presence of allergen-specific IgE antibodies is associated with allergic symptoms and the risk of systemic allergic reactions when the individual has a positive history of prior adverse reactions. The diagnostic value of IgE antibody measurements is thus limited to diseases in which the role of IgE has been documented (e.g., allergic rhinitis, atopic asthma, urticaria, and anaphylaxis to insect venoms, drugs, and foods). Because, allergen-specific IgE antibody can be detected in the skin or blood of an individual when no apparent allergy symptoms are manifested following allergen exposure, IgE antibody is considered necessary but not sufficient for allergic symptom expression. The clinical history must therefore always be considered when interpreting IgE antibody levels in the diagnostic process. Moreover, the translation of an IgE antibody response into a clinically evident allergic symptom following allergen exposure is known to be influenced by the patient's IgE antibody concentration, affinity and clonality, or specificity and IgE specific activity (specific IgE to total IgE ratio) (Christensen et al. 2008).

Cross-References

- Diagnostic Terms: Atopy
- Egg Allergy
- Food Allergies, Diagnostic Testing
- Food Allergy, Overview
- Genetic Regulation of IgE
- Hyper-IgE Syndrome
- IgE Isotype Switching
- IgE Receptor
- IgE Testing
- IgE-Secreting Plasma Cells
- Imported Fire Ant Allergy
- Methods (In Vivo): Skin Test (Intradermal, Puncture)
- Peanut Allergy
- Role of IgE in Disease
- Single-Plex Immunoassays and Autoanalyzers
- Specific IgE

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Analytes and Biomarkers: Nitric Oxide (NO) and Asthma

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Synonyms

Nitric oxide; Nitrogen monoxide (NO)

Definitions

Asthma is a heterogeneous disorder characterized by reversible airway obstruction, airway inflammation, and increased airway responsiveness whose severity can be measured through a marker of inflammation, nitric oxide, a free radical gas (NIH Expert Panel Report 3. 2007).

Introduction and Background

Nitric oxide (NO) is best known for the regulation of blood pressure through local relaxation effects on vascular smooth muscle when produced by vascular endothelial cells. NO is formed through an oxidation reaction by the conversion of arginine and oxygen (O_2) to citrulline by the three isoenzymes of nitric oxide synthase (NOS) via nicotinamide adenine nucleotide diphosphate (NADPH). Two of these isoenzymes (NOS1 and NOS3) are expressed constitutively, while NOS2 expression is induced in certain cell types such as macrophages by various inflammatory stimuli such as endotoxin or cytokines like interferon-γ (IFNγ) (Pollard et al. 2007). NO is a reactive oxygen that has a short half-life (few seconds) because it is generally inactivated by oxygen species. Thus, it must be produced continuously in order to act effectively as a signaling molecule (Pollard et al. 2007). The process evolves as follows: the release of intracellular Ca^{+2} activates NOS to generate nitric oxide. NO then binds to guanylyl cyclase leading to cyclic guanosine monophosphate (cGMP) which leads to smooth muscle cell relaxation.

In terms of its role in asthma, NOS isoforms are located in the bronchial epithelium, human alveolar epithelial cells, airway smooth muscle cells, nerves, and lung fibroblasts (Shaul et al. 1994; Pechkovsky et al. 2002; Fischer and Hoffmann 1996). High concentrations of NO are generated by macrophages via inducible nitric oxide synthase after stimulation by cytokines such as tumor necrosis factor-α (TNF-α), IFN γ, and interleukin-1β (IL-1β) to kill ingested microorganisms (Pollard et al. 2007, Barnes et al. 2008). This upregulation of inducible NOS in the setting of inflammation leads to increased production of NO which correlates with the observation that asthmatics have increased levels of exhaled nitric oxide (Hamid et al. 1993). Therefore, higher levels of exhaled nitric oxide correlate with higher levels of airway inflammation and poorer asthma control. Corticosteroids which reduce airway inflammation have been shown to decrease NO production (Massaro et al. 1995). Exhaled nitric oxide or the fractional concentration of exhaled nitric oxide (FeNO) has become a useful tool to aid the diagnosis of asthma, in part because it may also be helpful in the diagnosis of exacerbations of asthma and in providing the clinician with immediate, useful data.

Methods of Collection and Analysis

NO is reported as parts per billion (or nanoliters per liter) from exhaled breath. NO derived from the nasal passages is considered a contaminant as a high concentration of NO is present within the sinuses and nasal passages (Alving et al. 1993). There is a general consensus that in steroid-naïve asthma patients, 20–30 ppb demonstrates inflammation and therefore presence of asthma (9). FeNO can be measured by instruments such as a machine made by Aerocrine called NIOX or NIOX MINO (approved by the FDA in 2003). This is portable device that can be of benefit in the clinical setting as it provides immediate,

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real-time data (ATS/ERS guideline 2005). This real-time data is termed "online" measurement. In contrast, the term "offline" refers to exhalate collected from a vital capacity collection and analyzed at a later time. The latter method may be useful in patients that cannot actively participate in the testing (ATS/ERS guideline 2005).

When measuring exhaled NO, a noseclip should not be used as this can falsely increase the level of exhaled NO. Patients should be encouraged to maintain positive airway mouthpiece pressure during the exhalation phase. The measurement of NO in exhaled breath is affected by the flow rate, and it has been generally recommended that the ideal flow rate is 0.05 L/s over at least 6 s in patients >12 years of age. The patient will be asked to repeat this maneuver 3 times with at least 2 of these results having less than a 10 % difference. The concentration of NO is measured as a mean concentration at the plateau phase of the graph (when FeNO is graphed on the y-axis and time in seconds on the x-axis) over a 3 second portion (ATS/ERS guideline 2005).

Management

The current American Thoracic Society guidelines recommend that FeNO should be used as a marker of eosinophilic inflammation. Exhaled FeNO may not be useful in diseases that are nonallergic in nature and therefore are not responsive to treatment with steroids such as neutrophilic (steroid-resistant) asthma, COPD, or cystic fibrosis (Whelan and Silkoff 2008; Dweik et al. 2011). The current recommendations state that an FeNO of >50 ppb in patients >12 years of age (>35 ppb in children) indicates eosinophilic inflammation which may be amenable to treatment with steroids, while values of FeNO between 25 and 50 ppb for adults (between 20 and 35 ppb in children) should be carefully interpreted within the clinical setting (Whelan and Silkoff, 2008). It is suggested that a decrease of about 20 % of the FeNO value with steroid treatment indicates a significant response (Dweik et al. 2011).

Conclusions

NO is a biomarker for active eosinophilic inflammation in asthmatic subjects. The use of FeNO is useful in the assessment and treatment of asthma patients. It is helpful to first establish a baseline measure in patients and follow levels to assist the diagnosis of asthma exacerbations as well as response to treatment.

Cross-References

- Analytes and Biomarkers: Nitric Oxide (NO) and Asthma
- Asthma Variants: Allergic Asthma
- Asthma Variants: Cough-Variant Asthma
- Exhaled Nitric Oxide

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Analytes and Biomarkers: Precipitin Antibodies

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Synonyms

Double immunodiffusion; Ouchterlony

Definition

Precipitin is a reaction between an antibody and antigen that are distributed into separate wells in a gel, and they immunoprecipitate or produce a flocculate that is visible as a white precipitin line. Immune complexes form as they reach a point of equivalence at which the concentrations of antibody and antigen are optimal for producing maximal antigen–antibody cross-linking.

Introduction

In 1953, Ouchterlony published part of his thesis which described a method involving gels in which the addition of antigen and its respective antibody into separate wells caused them to diffuse toward each other (Ouchterlony 1953). As they reached a point called equivalence in which the concentrations of the antibody and antigen were optimal to maximize immune complex formation, a white flocculation occurred in the gel that could be seen by the naked eye as a white "precipitin" line. Ouchterlony originally used antigen from *Corynebacterium diphtheriae* and a corresponding immune serum from a horse immunized with this antigen. With this gel assay, Ouchterlony was able to ascertain information about the serological identity or nonidentity of the antigen. In his later work, he used egg albumin from various species (chicken, guinea hen, duck) and various rabbit anti-egg albumin preparations to show lines of identity and nonidentity.

Currently, the gel diffusion (Ouchterlony) test is considered a classic method for identifying IgG precipitating antibodies (precipitins) to those antigens associated with hypersensitivity pneumonitis and allergic bronchopulmonary aspergillosis. In 1972, precipitins were detected to mold hay in the serum of Farmer's lung patients (Pepys 1972). This finding has served to link hypersensitivity lung disease with an inhaled antigen and the presence of specific antibodies in the affected patient's serum. A positive precipitin test indicates the presence of relatively large amounts of antibody and is correlated with clinical evidence of hypersensitivity pneumonitis. Antigens such as thermophilic actinomycetes, fungi, and excreted animal protein have been identified and partially purified from organic dusts and implicated as causative agents for hypersensitivity

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pneumonitis (Fink et al. 1971; Reboux et al. 2007). In addition, positive precipitin tests (IgG antibody) and a positive skin test for IgE antibody to *Aspergillus* antigens together are correlated with allergic bronchopulmonary aspergillosis.

Double Immunodiffusion Assay

Technically, the assay utilizes an agarose gel plate with a patterned set of wells punched into the gel, each of which consists of a central well filled with the patient's serum, and eight smaller peripheral wells containing various types of antigens or control antisera, surrounding the central well. Because the antigen and serum diffuse radially toward each other, precipitating antibodies (mostly IgG) to a given antigen, if present in the serum, will lead to an antigen–antibody reaction which is evident as visible white bands or arcs that are formed between the two wells. When the lines produced by two antigen wells join after binding to antibody in the central well, they are lines of identity that verify the same antigen is in both wells. When they cross over each other, these are lines of nonidentity that verify the antigens in the two wells are of a different specificity (Fig. 1).

The extract–antigen preparations that are commonly used by laboratories to evaluate serum for precipitating antibodies include *Thermophilic actinomycetes* (*Micropolyspora faeni*, *Thermoactinomyces vulgaris*, *Thermoactinomyces candidus*), an *Aspergillus* panel (*Aspergillus fumigatus*, *Aspergillus niger*, *Aspergillus flavus*), pigeon serum, *Aureobasidium pullulans*, parakeet droppings, cockatiel droppings, parrot (Blue Front) droppings, and chicken droppings. Antibody-positive sera from animals (rabbits) or humans that are specific for each of the antigens run are used to quality control the assay. Lines of identity are verified by the joining of precipitin lines. The biotin-streptavidin system has also been applied to the precipitin analysis to enhance its performance (Novakovskiĭ et al. 2009).

Clinical Significance

Hypersensitivity pneumonitis (HP), also known as extrinsic allergic alveolitis, is a hypersensitivity reaction to antigenic organic dusts (e.g., molds, bird droppings) involving the lung interstitium and terminal bronchioles. Hours after a heavy antigenic exposure, an acute form of hypersensitivity pneumonitis can occur with chills, fever, malaise, cough, and shortness of breath. While histology of the lung lesions indicates a cell-mediated pathology, most patients with hypersensitivity pneumonitis have high levels of IgG antibody to the offending antigen in their serum. The gel diffusion method of measuring precipitating antibodies by diffusing antigen (extract) and antibody (control or patient's serum) toward each other in closely spaced wells in a porous agarose gel has been used to identify the presence of specific precipitating antibodies in the serum of HP patients. Precipitating antibodies or precipitins can be detected in the serum of nearly all ill patients but also in the serum of as many as 50 % of asymptomatic individuals who have been exposed to the relevant organic dusts. Immunoassays for IgG antibody to the appropriate organic dust antigens may be less useful clinically because they are too sensitive. They typically detect IgG antibody in sera of a much higher number of patients than the immunodiffusion methods, but they also generate a higher rate of false-positive results not related to clinical disease. Finally, the technique has been also applied to the detection of autoantibodies in the serum of patients with rheumatic disease (Koschik et al. 2012).

Limitations of Precipitin Analysis

The presence of precipitating antibodies against the offending antigen can be demonstrated in most patients with hypersensitivity pneumonitis. The presence of precipitins to *Aspergillus* antigens can be demonstrated in most patients with allergic bronchopulmonary aspergillosis.

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Precipitin Worksheet

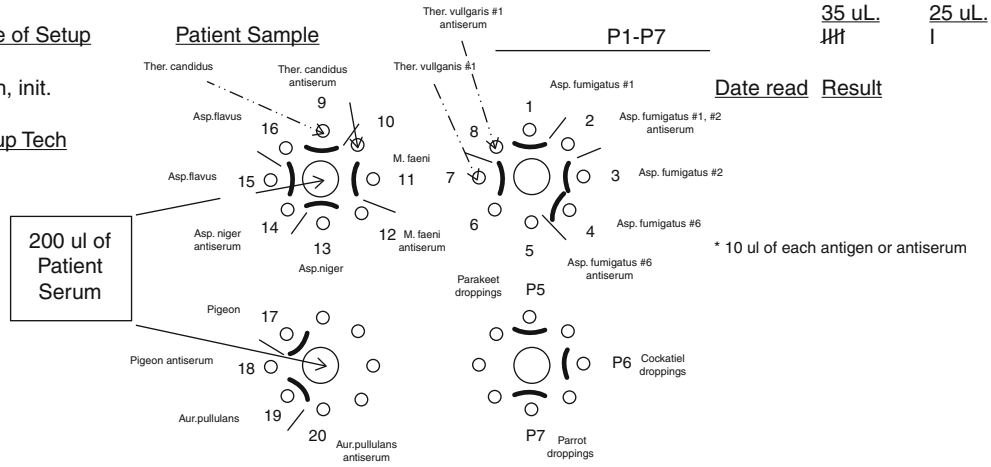
P2 1. Asp. fumigatus #1	P2 13. Asp. niger
2. Asp. fumigatus #1, #2 antiserum	14. Asp. niger antiserum
3. Asp. fumigatus #2	15. Asp. flavus
4. Asp. fumigatus #6	16. Asp. flavus antiserum
5. Asp. fumigatus #6 antiserum	P3 17. Pigeon serum
6. BLANK	18. Pigeon antiserum
P1 7. Ther. vulgaris #1	P4 19. Aur.pullulans
8. Ther. vulgaris #1 antiserum	20. Aur.pullulans antiserum
9. Ther. candidus	
10. Ther. candidus antiserum	P5 Parakeet droppings
11. M. faeni	P6 Cockatiel droppings
12. M.faeni antiserum	P7 Parrot droppings

Date Patient Acc.# Test

Date of Setup Patient Sample P1-P7 35 uL. 25 uL.

Tech, init. Date read Result

Setup Tech

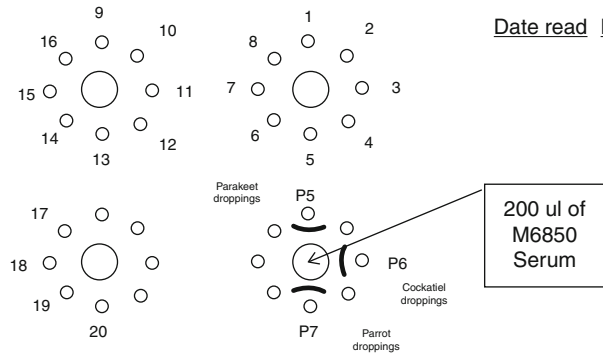


Date Patient Acc.# Test

Date of Setup M6850 (Bird Control) P5-P7 35 uL. 25 uL.

Tech. init. Date read Result

Setup Tech



Analytes and Biomarkers: Precipitin Antibodies, Fig. 1 Precipitin assay worksheet with schematic of positive control reactions

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A positive test can provide the physician with a diagnosis when supported by a history and clinical evidence. A positive test does not necessarily indicate hypersensitivity pneumonitis because asymptomatic individuals may develop precipitins without any features of the disease. Nor does the absence of precipitins eliminate the diagnosis because the precipitin test is an insensitive indicator of antibodies. Furthermore, precipitins are reduced or absent when the disease is not in an acute stage. Thus, a positive test for precipitating antibodies is quite helpful diagnostically but should be interpreted in the context of clinical findings. Occasionally, patients with hypersensitivity pneumonitis may have positive precipitins to several, apparently unrelated, antigens. It is not clear whether this is related to cross-reactivity and/or to the high levels of total IgG in these patients.

Cross-References

- ▶ Allergen Avoidance: Fungi and Mold Avoidance
- ▶ Asthma Variants: Allergic Asthma
- ▶ Autoimmune Lung Disease

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Anaphylaxis, Background

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Synonyms

Anaphylactic reaction; Anaphylactic shock; Anaphylactoid reaction; Life-threatening allergy

Background

The death of Pharaoh Menes (in 2641 BC) following an insect sting is believed to be one of the first recorded cases of anaphylaxis (Kruszewski 2003). In 1902, the French physiologists Charles Richet and Paul Portier coined the term "anaphylaxis" – *ana* meaning "the opposite of" and *phylaxis* meaning "protection" (Lieberman 2013). This was based on the observation that dogs reinjected with toxins from sea anemones suffered rapid deaths, this despite being injected with a smaller second dose. They were at the time trying to develop a vaccination that would protect against the sting of the sea anemone (Cohen and Zelaya-Quesada 2002). In 1913, Richet was awarded the Nobel Prize in Physiology or Medicine for his work on the discovery of anaphylaxis (Nobel Prize 1913).

Definition

There is no universally accepted definition of anaphylaxis. Several working definitions have however been formulated to aid clinical diagnosis and management of anaphylaxis (American Academy

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of Pediatrics 1990; International Collaborative Study of Severe Anaphylaxis 1998; Australasian Society of Clinical Immunology and Allergy Inc 2004; Joint Task Force on Practice Parameters 2005). It has, for example, been defined as a "severe, life-threatening generalized or systemic hypersensitivity reaction" by the European Academy of Allergology and Clinical Immunology (EAACI 2014) (Johansson et al. 2004; Muraro et al. 2007). The Anaphylaxis Working Group of the Resuscitation Council (UK) drew attention to key clinical features that can help in the recognition and diagnosis of anaphylaxis by adding: "This is characterized by rapidly developing life-threatening airway and/or breathing and/or circulation problems usually associated with skin and mucosal changes" (UK Resuscitation Council 2008).

Although relatively uncommonly encountered, anaphylaxis is a life-threatening emergency that all healthcare professionals need to be able to diagnose and manage. Prompt recognition and appropriate emergency management with epinephrine are key to saving lives. Careful post-event planning with follow-up by an allergy specialist is important in facilitating detailed assessment to minimize the risk of further reactions and preparing individuals to appropriately manage any future episodes of anaphylaxis. Subsequently, we describe the epidemiology, etiology, pathophysiology, and management of this condition.

Epidemiology

Studying the epidemiology of anaphylaxis is complicated by the lack of an internationally agreed definition, its relatively low incidence, and the fact that most episodes are short lived (Simons and Sheikh 2007). Notwithstanding these challenges, the American College of Allergy, Asthma and Immunology Epidemiology of Anaphylaxis Working Group has estimated that the cumulative incidence of anaphylaxis was 50–2,000 episodes per 100,000 persons or a lifetime prevalence of 0.05–2.0 % (Lieberman et al. 2006). More recently, an EAACI systematic review found that the incidence of anaphylaxis in Europe ranged from 1.5 per 100,000 person-years to 32 per 100,000 person-years (Larenas Linnemann et al. 2008; Amin and Davis 2012; Panesar et al. 2013). The pooled lifetime prevalence was estimated at 0.3 % (95 %CI 0.1–0.5).

The limited available data on anaphylaxis trends over time suggest that the incidence of anaphylaxis may be increasing (Sheikh and Alves 2001; Gupta et al. 2004; Gupta et al. 2007; Lin et al. 2008; Poulos et al. 2007). This body of epidemiological work has also demonstrated that anaphylaxis can affect males and females of any age or ethnic or social group (Sheikh and Alves 2001). The risk of fatality is low with a case fatality ratio of <1 % (Lieberman et al. 2006; Panesar et al. 2013). It is, however, difficult to predict those at the greatest risk of fatality.

Patient risk factors for anaphylaxis include vulnerability owing to age or physiological state. Asthma and cardiovascular disease and drugs such as beta-adrenergic blockers and angiotensin converting enzyme inhibitors also increase the risk of very severe/fatal reactions. Cofactors that can amplify anaphylaxis include exercise, infection, and emotional stress (see Box 1) (Simons and Sheikh 2013).

Box 1: Patient Risk Factors for Anaphylaxis

Age related factors

- Infants: anaphylaxis can be hard to recognise, especially if the first episode; patients cannot describe symptoms
- Adolescents and young adults: increased risk taking behaviours such as failure to avoid known triggers and to carry an adrenaline autoinjector consistently
- Pregnancy: risk of iatrogenic anaphylaxis – for example, from β lactam antibiotics to prevent neonatal group B streptococcal infection, agents used perioperatively during caesarean sections, and natural rubber latex
- Older people: increased risk of death because of concomitant disease and drugs

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Concomitant diseases
- Asthma and other chronic respiratory diseases
- Cardiovascular diseases
- Mastocytosis
- Allergic rhinitis and eczema[a]
- Depression, cognitive dysfunction, substance misuse

Drugs
- β adrenergic blockers[b]
- Angiotensin converting enzyme (ACE) inhibitors[b]
- Sedatives, antidepressants, narcotics, recreational drugs, and alcohol may decrease the patient's ability to recognise triggers and symptoms

Cofactors that amplify anaphylaxis
- Exercise: anaphylaxis associated with exercise may be food dependent or food independent: non-steroidal anti-inflammatory drugs and other listed cofactors may also be relevant
- Acute infection such as an upper respiratory tract infection
- Fever
- Emotional stress
- Disruption of routine – for example, travel and jet lag
- Premenstrual status in women and girls

[a]Atopic diseases are a risk factor for anaphylaxis.triggered by food, latex, and exercise, but not for anaphylaxis triggered by most drugs or by insect stings.

[b]Patients taking β adrenergic blockers or ACE inhibitors seem to be at increased risk for severe anaphylaxis. In addition, those taking β adrenergic blockers may not respond optimally to adrenaline treatment and need glucagon, a polypeptide with non-catecholamine dependent inotropic and chronotropic cardiac effects, atropine for persistent bradycardia, or ipratropium for persistent bronchospasm.

Source: Reprinted with permission from Simons and Sheikh (2013)

Cross-References

- ▶ Anaphylaxis, Clinical Manifestations and Diagnosis
- ▶ Biphasic, Protracted, and Late-Phase Reactions in Anaphylaxis
- ▶ Etiology of Anaphylaxis
- ▶ Management of Anaphylaxis
- ▶ Mast Cell Mediators Associated with Anaphylaxis
- ▶ Pathophysiology of Anaphylaxis

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Anaphylaxis, Clinical Manifestations and Diagnosis

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Synonyms

Anaphylactic reaction; Anaphylactic shock; Anaphylactoid reaction; Life-threatening allergy

Definition

The cutaneous, respiratory, cardiovascular, and gastrointestinal systems are the most commonly affected, but reactions may also involve other organ systems. Common clinical features include flushing, urticaria, angioedema, and pruritus; laryngeal edema, cough, wheeze, and dyspnea; hypotension, cardiac arrhythmias, syncope, shock, and cardiac arrest; abdominal cramping with nausea, vomiting, and diarrhea; and a feeling of impending doom. Other symptoms

Anaphylaxis, Clinical Manifestations and Diagnosis, Table 1 Clinical criteria for diagnosing anaphylaxis

Anaphylaxis is highly likely when any *one* of the following three criteria are fulfilled:
1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (e.g., generalized hives, pruritus or flushing, swollen lips-tongue-uvula)
And at least one of the following
(a) Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
(b) Reduced BP or associated symptoms of end-organ dysfunction (e.g., hypotonia [collapse], syncope, incontinence)
2. Two or more of the following that occur rapidly after exposure to a *likely allergen for that patient* (minutes to several hours):
(a) Involvement of the skin-mucosa tissue (e.g., generalized hives, itch-flush, swollen lips-tongue-uvula)
(b) Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
(c) Reduced BP or associated symptoms (e.g., hypotonia [collapse], syncope, incontinence)
(d) Persistent gastrointestinal symptoms (e.g., crampy abdominal pain, vomiting)
3. Reduced BP after exposure to *known allergen for that patient* (minutes to several hours):
(a) Infants and children: low systolic BP (age specific) or greater than 30 % decrease in systolic BP[a]
(b) Adults: systolic BP of less than 90 mmHg or greater than 30 % decrease from that person's baseline

Source: Reprinted with permission from Sampson et al. (2006)
[a]Low systolic blood pressure for children is defined as less than 70 mmHg from 1 month to 1 year, less than (70 mmHg + [2 × age]) from 1 to 10 years, and less than 90 mmHg from 11 to 17 years
PEF Peak expiratory flow, *BP* blood pressure

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Anaphylaxis, Clinical Manifestations and Diagnosis, Table 2 Differential diagnosis of anaphylaxis

Condition	Differentiating signs/symptoms
Septic shock	Absence of previous allergic reactions, lack of allergen exposure, slower onset, fever, and other signs of localized infection often differentiate septic shock from anaphylaxis
Cardiogenic shock	Age, risk factors for coronary artery disease, previous angina episodes, absence of an allergic history, no indication of allergen exposure, typical cardiac signs and symptoms (such as chest pain on exercise) help to distinguish. Severe anaphylactic reactions can trigger cardiac events
Hypovolemic shock	Water or fluid loss occurs via heat exposure, profuse sweating, significant blood loss, vomiting, and diarrhea. Patients report thirst and a drop in urinary output. Anaphylaxis is a form of hypovolemic shock secondary to intravascular fluid shifts. Establishing an alternative cause of hypervolemia will differentiate from anaphylaxis
Vasovagal reaction	The characteristic feature is hypotension, with pallor, weakness, nausea, vomiting, and diaphoresis. The sudden onset, the cardiovascular collapse, and unconsciousness are all also typical of anaphylaxis. May be differentiated by the lack of cutaneous manifestations, the absent allergic history, and the presence of bradycardia instead of tachycardia, even though can be either absent or misleading
Asthma	Absence of allergen exposure, or of cutaneous or digestive findings, and a hx of previous asthma episodes help to differentiate. A rapid onset is suggestive of anaphylaxis and should at least trigger referral to higher-level medical care
Acute chronic obstructive pulmonary disease exacerbation	Absence of allergen exposure, or of cutaneous or digestive findings, and a hx of established chronic lung disease help to differentiate
Hereditary angioedema	Characterized by recurrent episodes of slowly progressing angioedema of the skin, mucosa, and submucosal tissue. There is no urticaria, hypotension, or history of allergen exposure as in anaphylaxis. FHx is positive
Vocal cord dysfunction aspiration	Cutaneous signs, digestive findings, hypotension, and allergen exposure are not present
Foreign body aspiration	No allergen exposure, no cutaneous or digestive findings, but a hx of foreign body aspiration differentiates this diagnosis
Monosodium glutamate (MSG) ingestion	In reaction to MSG exposure, the following MSG symptom complex may occur. One or more of the following are present: burning sensation in the back of the neck, forearms, and chest; numbness in the back of the neck, radiating to the arms and back; tingling, warmth, and weakness in the face, temples, upper back, neck, and arms; facial pressure or tightness; chest pain; headache; nausea; rapid heartbeat; bronchospasm; drowsiness; and weakness. No urticaria, angioedema, or hypotension occurs
Carcinoid syndrome	On examination, there is an associated right heart murmur
Postmenopausal hot flushes	Flush appears several times a day and lasts for 4–5 min. There are no respiratory tract symptoms and no hypotension
Red man syndrome	This syndrome usually appears within 4–10 min after start or soon after the completion of a vancomycin infusion. It is characterized by flushing and/or an erythematous rash that affects the face, neck, and upper torso. Hypotension and angioedema may also occur, but less frequently
Panic disorder	In some, functional stridor develops as a result of forced adduction of the vocal cords; however, no urticaria, angioedema, or hypotension occurs
Scombrotoxic food poisoning	Symptoms resemble IgE-mediated food allergy, but most prominent on the upper torso and face. Erythematous rash, but no urticaria noted. Resolves untreated within 12 h

Source: Reprinted with permission from BMJ Best Practice (2011)

and signs can include rhinorrhea, dysphonia, metallic taste, uterine cramps, light-headedness, and headache (Simons et al. 2012). The most important clinical features are summarized in the diagnostic criteria proposed by Sampson et al. 2006 (see Table 1).

The differential diagnosis of anaphylaxis is important and includes many conditions such as those shown in Table 2 (Best Practice 2011).

The diagnosis of anaphylaxis is primarily a clinical one; the most common criteria used are those proposed by Sampson et al. (2006).

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Cross-References

- ▶ Anaphylaxis, Background
- ▶ Biphasic, Protracted, and Late-Phase Reactions in Anaphylaxis
- ▶ Etiology of Anaphylaxis
- ▶ Management of Anaphylaxis
- ▶ Mast Cell Mediators Associated with Anaphylaxis
- ▶ Pathophysiology of Anaphylaxis

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Articaine Allergic Reaction

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Synonyms

Allergy; Local anesthetics

Local anesthetics (LA) prevent neural conduction by blocking sodium channels of neural synapses. Two classes of LA can be distinguished depending on their pharmacological structure, amides and esters. While amides (to which articaine belongs) are widely used as LA in dentistry, surgery, and during the initiation of general anesthesia, esters are rarely applied, mostly in topical preparations. Allergic reactions to LA include anaphylaxis, due to either IgE-mediated (type I by Coombs and Gell) or non-IgE-mediated, pseudo-allergic immune mechanisms, and eczema, caused by delayed-type hypersensitivity reactions (type IV by Coombs and Gell). Diagnostic evaluation encompasses skin prick and intradermal tests, patch tests (for the later), and where appropriate subcutaneous provocation test including other LA serving as potential substitutes, since cross-reactivity is rarely the case in particular for amides.

Cross-References

- ▶ Role of IgE in Disease

Aspirin-Exacerbated Respiratory Disease

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Synonyms

AERD: Samter's triad, aspirin-intolerant asthma, triad asthma; Antileukotrienes: leukotriene receptor antagonist; Aspirin desensitization: aspirin tolerance induction

Definition

The association between asthma, nasal polyposis, and aspirin sensitivity has been observed for

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almost a century, but this syndrome gained more widespread recognition after publication of the work of Max Samter in 1968. Thereafter, this syndrome has been known as Samter's triad or aspirin-exacerbated respiratory disease (AERD). AERD is characterized by an intense eosinophilic and mast cell inflammatory process. The initiating insult has yet to be found, but some theories include viral infection and exposure to air pollution or tobacco smoke. Aspirin itself has not been implicated as the instigating factor for this inflammatory process, as the inflammation is ongoing before the first aspirin-induced reaction.

Essay

Epidemiology, Pathophysiology, and Diagnosis Epidemiology

The association between asthma, nasal polyposis, and aspirin sensitivity has been observed for almost a century, but this syndrome gained more widespread recognition after publication of the work of Max Samter in 1968 (Samter and Beers 1968). Thereafter, this syndrome has been known as Samter's triad. Though several different names and acronyms have been used to identify Samter's triad, throughout this short review, the term aspirin-exacerbated respiratory disease, or AERD will be used.

The prevalence of AERD is variable depending upon what group is being studied and how AERD is being determined, based on prior history or drug challenge. In a meta-analysis of several studies, which used oral aspirin challenge to prove the diagnosis of aspirin sensitivity in asthmatics, the combined prevalence was 21 % in adults and 5 % in children (ages 0–18) (Jenkins et al. 2004). The potential pool of patients is further enriched if one looks at asthmatic patients also diagnosed with nasal polyposis or chronic sinusitis; in this subset of patients, the prevalence of aspirin sensitivity was reported to be as high as 30–40 % (Stevenson and Szczeklik 2006).

Pathophysiology

First, special mention should be made that AERD is not a true allergy. The term allergy should be reserved for an antigen-specific IgE-mediated hypersensitivity reaction. Instead, AERD is characterized by an intense eosinophilic and mast cell inflammatory process. The initiating insult has yet to be found, but some theories include viral infection and exposure to air pollution or tobacco smoke (Stevenson and Szczeklik 2006). Aspirin itself has not been implicated as the instigating factor for this inflammatory process, as the inflammation is ongoing before the first aspirin-induced reaction.

Patients with AERD often react to both aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs), a reaction that is driven by the ability of these drugs to inhibit the enzyme cyclooxygenase 1 (COX-1). One theory proposes that alterations in the balance of the prostaglandin and leukotriene pathway lead to the AERD phenotype. Most AERD patients have elevated baseline levels of the leukotriene products, as measured by urinary excretion of leukotriene E_4; once challenged with aspirin, these levels are further increased (Sanak et al. 2004). Elevated cysteinyl leukotriene (cysLT) levels have also been identified in patients with chronic rhinosinusitis (CRS) with and without nasal polyps, regardless of AERD status. Additional research has demonstrated increased expression of the cysteinyl leukotriene 1 receptor ($cysLT_1$) on leukocytes infiltrating sinonasal mucosa from patients with AERD and nasal polyps (Sousa et al. 2002; Ozen et al. 2007). Thus, both increased cysLT synthesis and increased receptor expression may contribute the pathogenesis of this process.

Assessment and Diagnosis

History alone is not sufficient to make the diagnosis of AERD. The best way to assess a patient for AERD is through aspirin challenge, as there are currently no reliable in vitro surrogates. Aspirin challenge can be done a number of different ways, depending on the route of administration and the challenge drug. In the United States, oral administration is most common. Patients are challenged with increasing doses of aspirin, starting with a dose around 40.5 mg to a top dose of 650 mg. Lung function and symptoms

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are followed after each dose. A positive challenge is defined by a significant drop in FEV_1 and/or the appearance of naso-ocular symptoms. In Europe, aspirin lysine is used in both bronchial and nasal challenges; however, because it is not approved for use in human subjects by the US Food and Drug Administration, it is not available for use in the United States.

Management Medical Therapy

Avoidance of COX-1 inhibitors is paramount. Patients need to be especially careful of any over-the-counter medications, which may contain aspirin or other NSAIDs. For example, some Alka Seltzer™ products contain 325–500 mg of aspirin. In contrast to the cross-reactivity of COX-1 inhibitors, COX-2 inhibitors have been shown to be relatively safe. Although the package inserts of COX-2 inhibitors advises against using such drugs in aspirin-intolerant patients, several studies have shown with a greater than 95 % confidence that these agents can be used in patients with AERD (Simon 2004). Acetaminophen is a weak COX-1 inhibitor. Patients with AERD can usually tolerate doses of up to 650 mg; however, at the higher dose of 1,000 mg, 20 % of patients may have a reaction (Settipane et al. 1995).

As patients with AERD have markedly elevated leukotrienes, therapy to block production or action of these mediators would seem to be a logical strategy. In the United States, there are two types of antileukotriene therapy approved by the FDA for use in the treatment of asthma. The first, zileuton (Zyflo®), is an inhibitor of the enzyme 5-lipoxygenase and partially blocks conversion of arachidonic acid to leukotriene A_4. Zileuton has been shown to decrease the number of asthma exacerbations, improve pulmonary function, improve sense of smell, and decrease nonspecific bronchial hyperreactivity to histamine (Dahlen et al. 1998). Montelukast (Singulair® 10 mg daily) and zafirlukast (Accolate® 20 mg daily) are examples of the second class of antileukotriene therapy. They act downstream of zileuton and work by competitively binding to the $cysLT_1$ receptor. In a double-blind placebo-controlled trial, montelukast was found to increase pulmonary function, decrease asthma symptoms, and improve asthma-specific quality of life (Dahlen et al. 2002). In practice, clinical effects of these treatments seem to vary widely.

Inflammation of the upper airway may contribute to poor control of the lower airway. As such, these patients should receive aggressive treatment of polyposis with high-dose intranasal steroids, nasal saline rinses, and selective use of oral corticosteroids. In refractory cases, systemic corticosteroids of variable duration may be required to control disease and improve quality of life. Antibiotics are reserved for acute bacterial exacerbations of sinonasal disease but should be used selectively. Treating the underlying mucosal inflammation is the most important step in patient management. Too often, anti-infective medications are prescribed as the sole therapy in patients with hyperplastic or polypoid rhinosinusitis.

Treatment of an acute aspirin-induced lower respiratory reaction is best treated with nebulized albuterol. Repeat doses can be given every 5–10 min until improvement of symptoms. Laryngospasm is treated with either subcutaneously injected epinephrine or inhaled racemic epinephrine. An acute increase in nasal congestion responds to topical decongestants such as oxymetazoline. Oral antihistamines and oral decongestants may also be helpful. In the event of severe symptoms, intubation, mechanical ventilation, and intensive care monitoring are appropriate.

ASA Desensitization

Aspirin desensitization should be considered as add-on therapy in patients not adequately controlled with traditional medical management or in those patients who require aspirin or NSAID treatment for other medical conditions. Desensitization to aspirin not only allows the patient to safely take aspirin but also allows them to tolerate therapeutic doses of other cross-reacting NSAIDs. Long-term results of aspirin desensitization are favorable. In one study, after the first 6 months of treatment, several clinical markers were significantly better: fewer number of sinus

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infections, improved sense of smell, and improved nasal and asthma symptoms. After at least 1 year of follow-up, not only were these benefits sustained, but the authors report improvement in several other clinical markers: fewer sinus operations, hospitalizations for asthma, and emergency department visits for asthma. Corticosteroid use, including intranasal, inhaled, and oral systemic steroids, were all diminished after at least 1 year of treatment, compared to baseline (Berges-Gimeno et al. 2003).

Because severe asthma exacerbations may occur during the desensitization procedure, patients should be well informed of these risks. Also, patients should have stable, controlled asthma prior to the procedure.

Surgical Management

Endoscopic sinus surgery (ESS) remains the treatment of choice for medically refractory CRS with and without nasal polyposis. Since its introduction in the 1980s, ESS has undergone review, reassessment, and substantial refinement confirming its role in the management of CRS. When considering a wide range of patient subgroups, overall success rates have been reported to range from 85 % to 97 % (Levine 1990; Kennedy 1992; Senior et al. 1998; Metson and Gliklich 2000; Poetker and Smith 2007).

Assessing the impact of ESS on patients with AERD and nasal polyps remains problematic, largely due to limited published data. Nakamura et al. prospectively evaluated the impact of traditional and endoscopic sinus surgery on 22 patients with AERD (Nakamura et al. 1999). Overall patients benefited from surgical interventions, though validated outcome measures were not used, and no comparison group was included.

The impact of ESS on asthma outcomes in patients with AERD is even less well defined. Two published studies have attempted to explore this issue. Nakamura et al. retrospectively evaluated the asthma component in patients with AERD one year after ESS (Nakamura et al. 1999). These authors reported improvement in 91 % of patients, both subjectively and based on pulmonary function testing. However, follow-up was only one year, and a comparison group was not included. More recently, Loehrl et al. published their retrospective review of 31 patients with AERD having undergone ESS. This retrospective study used a standardized survey and had a mean follow-up of 10 years. Overall 94 % of patients reported long-term postoperative improvement in their asthma symptoms and 68 % reported additional improvement beyond the first postoperative year. Emergency department visits and inpatient hospitalizations decreased for this cohort. The weaknesses of this study, however, are the lack of control group and the retrospective design. Nonetheless, this data suggests a potential benefit in asthma outcomes in patients with AERD undergoing ESS for CRS (Loehrl et al. 2006). This is similar to the data in asthmatics without AERD (Smith et al. 2005).

Conclusions

In the subset of patients with AERD, management is especially challenging. The balance of pro-inflammatory leukotrienes and anti-inflammatory prostaglandins appears to be important in the pathogenesis of the disease. Agents targeted at disruption of the leukotriene pathway appear to be effective in some patients. Aspirin desensitization is a specialized procedure that allows patients with AERD to safely tolerate aspirin and other cross-reacting NSAIDs. The benefits of long-term aspirin therapy following desensitization include better control of both the upper and lower airway disease and should be considered as add-on therapy in those patients not controlled with traditional medical management. Equally, ESS should be considered as part of the patient's overall disease management. Once considered controversial or even detrimental, ESS is now thought to contribute to better control of sinonasal and asthma disease. Taken as a whole, a combined medical and surgical approach, with collaboration from family medicine specialists, pulmonary specialists, allergists, internists, and otolaryngologists, should lead to better patient clinical outcomes.

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Cross-References

- Analytes and Biomarkers: IgE
- Eosinophil Historical Background
- Eosinophil, Definition and Morphology
- Mast Cells, Growth and Development

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Assay Performance Parameters

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Synonyms

Analytical sensitivity; Analytical specificity; Cross-reactivity; Linearity; Nonspecific binding; Parallelism; Precision; Recovery; Reproducibility

Definition

The analytical performance of a laboratory assay can be documented by defining its (a) analytical sensitivity or detection limit, (b) the extent of nonspecific binding which is determined by matrix effects associated with the specimen and assay buffers, (c) specificity for the target analyte as assessed by competitive inhibition, (d) cross-reactivity with molecules structurally similar to the target analyte, (e) linearity or parallelism

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between the reference and unknown test specimen dilution curves, (f) precision or agreement within assays, (g) reproducibility or agreement between assay runs, and (h) recovery or its ability to quantitatively detect the level of analyte that has been intentionally added or spiked into a test specimen. Each of these interwoven parameters will be discussed in this section.

Introduction

A clinical laboratory test involves a set of reagents, typically an antibody and antigen, that are added together in a reaction vessel. The concentrations of the reagents are optimized to permit the assay to detect an analyte which can either be an antigen or antibody. The assay ultimately generates a response measurement based on the remaining radioactivity, color, fluorescence, or chemiluminescence. The response is plotted against a known amount of the analyte in a standard or calibrator to create a standard curve, from which test specimen response data are interpolated into estimates of dose (Butler and Hamilton 1991). Each assay displays a set of parameters that allow the laboratorian to determine if the assay meets generally accepted performance guidelines for a clinically relevant test (Matsson et al. 2008). These performance parameters are discussed in this section together with benchmark targets for a suitable laboratory test.

Analytical Sensitivity

The minimum detectable dose of an analyte in an assay system is also called its positive threshold, positive cut point, or analytical sensitivity. It is the smallest quantity of an analyte that can be reproducibly and statistically distinguished from the background or a zero calibrator in a given assay system. Often times, this minimum detectable concentration is identified using a 95 % confidence interval around a zero calibrator which is devoid of analyte. If one assumes an adequate number of test samples and that their distributions are similar (e.g., an equivalent distribution between the 0 calibrator and low positives), the 95 % confidence interval means 3.3 standard deviations between the mean levels produced by the 0 calibrator and the low positives. The positive cutoff level should, therefore, be greater than 3.3 SD from the mean of the 0 calibrator. The analytical sensitivity is often computed as the upper limit of the 95 % confidence interval of the mean level produced by the 0 calibrator based on 20 replicates of at least two negative serum controls or negative serum pools in five assays (100 measurements). As an illustration, the analytical sensitivity of the IgE antibody assays on the 3 clinically used autoanalyzers is 0.1 kU/l where 1 unit = 2.4 μg of IgE. The analytical sensitivity of an assay can be practically determined by computing the slope of the calibration curve and determining the ability of an analytical procedure to produce a measurable change in the signal for a defined change of the quantity.

Nonspecific Binding

Nonspecific binding or NSB is the attachment of an analyte that is not attributable to specific binding to a receptor or antibody. NSB is commonly detected as the background signal in an immunoassay that is derived from the nonspecific association of the signal generator with other reactants or the reaction vessel itself. NSB can be minimized by adding an irrelevant protein such as bovine serum albumin to the assay buffer. The importance of nonspecific binding rests in its effect on the analytical sensitivity of an assay. As the nonspecific binding level in the assay increases, the lower limit of the analyte that the assay can detect decreases. In current IgE antibody assays, nonspecific binding is largely determined by the total level of IgE in a specimen.

The matrix of an assay reaction mixture describes all of the components of a material system, except the analyte. In a given assay, the matrix of the calibrator, standard, and the test specimens should be comparable. This will optimize the assay performance by maximizing parallelism and ensuring that the level of nonspecific

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binding is comparable between the calibration and test specimen portions of the assay (Butler and Hamilton 1991). For instance, serum from a non-atopic person that is devoid of IgE is considered an ideal diluent or protein matrix for IgE antibody assays.

Analytical Specificity

The assay's analytical specificity defines the ability of an analytical method to measure only the target component it purports to measure. For allergy tests involving IgE antibody quantification, specificity refers to an assay that is specific for IgE and shows no cross-reactivity of the anti-human IgE reagent with other classes of human antibodies (e.g., IgG, IgA, IgM, and IgD). Specificity of an allergen-specific IgE antibody assay can be analytically demonstrated by showing complete inhibition of binding of IgE antibody after the relevant soluble allergen is added to the IgE antibody containing serum before it is analyzed in the assay that uses the same allergen on a solid phase as one of its reagents. Importantly, potentially interfering substances including, but not limited to, lipids, hemoglobin, and medications commonly used by allergic patients and any other potentially interfering substance should be identified to the laboratorian.

Cross-Reactivity

In immunology, cross-reactivity is a term that indicates an interaction of an antibody with an antigen other than the one that elicited its formation. This binding occurs as a result of shared, similar, or identical antigenic determinants or epitopes on the molecule. Human IgE antibody for instance may bind to an allergenic epitope that is structurally similar to, but not identical with, the molecule that elicited its formation. An illustration of allergenic cross-reactivity is the ability of IgE anti-birch pollen that is specific for an epitope on the group 1 birch pollen allergen Bet v 1 to bind Cor a 1, the group one allergen from hazelnut (Sicherer et al. 2008) or Ara h 8 from peanut or Mal d 1 from apple. The extent of cross-reactivity impacts on the overall analytical sensitivity of an assay.

Depletion Analysis

Depletion analysis is an analytical procedure that is used to estimate the quantity of antibody in a prospective calibrator or reference preparation. Using short ragweed as an illustrative allergen specificity, an IgE anti-ragweed-containing serum is first preabsorbed with either ragweed-solid phase or a sham-solid phase. Three aliquots of the same serum (unabsorbed, sham-absorbed, and ragweed-absorbed) are then analyzed for their total serum IgE content. The difference in the total IgE levels between the sham- and ragweed-absorbed serum represents the amount of specific IgE that was depleted or removed from the serum by the solid-phase allergen (Butler and Hamilton 1991). The sham-adsorbed IgE antibody levels should be equivalent to IgE anti-ragweed content in the unabsorbed serum. Elution and analysis of the ragweed-solid phase adsorbed IgE antibody can be added to the procedure to add a level of confidence to the specific antibody estimation.

Linearity (Parallelism)

Linearity is a property of a quantitative assay which insures that (within a defined analyte working range) the assay provides results that are directly proportional to the concentration or amount of analyte in the test sample. As the test sample and calibrator or reference serum are diluted out, their assay response signals need to parallel each other in order for the assay to be considered linear. Linearity refers to the overall system response. Moreover, parallelism describes the extent to which the dose–response relationship between two materials (i.e., calibrator vs. unknown specimens) is constant for the examined range of concentrations. Desired parallelism is demonstrated by analysis of multiple dilutions of serum in the same assay run. Low inter-dilutional

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"dose" coefficients of variation (e.g., <15 % CV) provide evidence that the calibrator and test portions of the immunoassay are parallel.

Precision (Intra-assay Variance) and Reproducibility (Inter-assay Variance)

Precision defines the agreement of replicate measurements of a given specimen within a single assay run. It represents the extent of closeness of agreement between independent replicate test results that were obtained in the same assay run. Precision does not have a numerical value. Rather, it is expressed in terms of imprecision of the assay such as the coefficient of variation which is the standard deviation divided by the mean of replicate dose measurements. Precision for an assay can be represented by a precision profile plot. The precision profile displays the precision (intra-assay CV) of an assay across the analyte concentration range of interest. More specifically, plotting the CVdose (Y-axis) against the dose (X-axis) provides precision profile or alternatively called an imprecision profile.

In contrast to precision, reproducibility defines the agreement of replicate measurements of a given specimen between runs of the same assay. It represents the extent of closeness of agreement between independent test results that were obtained in the same assay system on different days. Reproducibility is also expressed in terms of imprecision by an inter-assay coefficient of variation. A precision profile plot can also be used to display the reproducibility of an assay in which the same test sera are analyzed on different days.

Recovery

Recovery describes the ability of an assay to quantitatively detect the level of analyte that has been intentionally added or spiked into a test specimen. It involves detecting a measurable increase in the analyte concentration in a sample after adding a known amount of an identical substance directly to the specimen. Both unspiked and spiked serum specimens are analyzed in the assay and the proportion of the analyte that is detected over preexisting analyte levels is compared to the amount added. An assay's recovery of 100 % is ideal.

Summary

When evaluating whether an assay is suitable for use in a clinical laboratory, a number of analytical parameters are used to assess the assay's performance. They describe the assay's lower limit of detection or sensitivity, the extent to which the assay specifically detects the intended analyte or cross-reacts with structurally similar molecules, its variance both within and between assays, and its quantitative properties in terms of displayed linearity or parallelism between the calibrator and test specimens. An assay that displays an acceptable working range within the therapeutic window of the analyte, has low nonspecific binding properties, and has good intra-assay and inter-assay coefficients of variation typically less than 10 % and 15 %, respectively, is an assay worth consideration for a clinical laboratory.

Cross-References

- ▶ Analytes and Biomarkers: Environmental Allergen Assessment
- ▶ Analytes and Biomarkers: IgE
- ▶ Cotinine
- ▶ Food Allergies, Diagnostic Testing
- ▶ IgE Testing
- ▶ Methods (In Vitro and In Vivo): Nephelometry and Turbidimetry
- ▶ Methods (In Vivo): Skin Test (Intradermal, Puncture)
- ▶ Single-Plex Immunoassays and Autoanalyzers

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Asthma Variants: Allergic Asthma

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Definition

Asthma is an inflammatory disorder of the airways, characterized by hyperresponsive airways that exhibit reversible airflow obstruction. A subset of patients with asthma have asthma that is triggered, or kept inflamed, by allergens. The body has an inappropriate immune response to environmental triggers (Lewkowich and Wills-Karp 2008). These allergens can include dust mite, cockroach, animal hair and dander, pollens, and molds. Cat and dust mite are the most common allergens (Lugogo et al. 2010). Studies have shown that children who are younger than 5, recurrent wheezers, and already sensitized to allergens are more likely to have persistent asthma and reduced lung function as they get into later childhood (Guilbert et al. 2008). A US study (Childhood Asthma Management Program) of 5–12-year-old asthmatic children revealed inhalant allergen sensitization in 88 % of the study participants on allergen skin prick testing (Liu et al. 2011), indicating that allergen sensitivity is a major presence in the childhood asthmatic population.

Scientific Background of Allergic Asthma

Studies have pointed to T-cell mediators as playing a central role in allergic asthma. Specifically there is a shift toward Th2 cells and cytokines, specifically IL-4, IL-5, IL-13, and IL-9. These cytokines in turn regulated the production of IgE and the recruitment of effector cells, including mast cells, eosinophils, fibroblasts, and epithelial cells. Studies in mice have also pointed to impaired function of T regulatory cells (Treg), in the loss of normal tolerance for allergens; this may be another point at which therapeutics could be developed, aimed at enhancing Treg function for asthmatics (Lewkowich and Wills-Karp 2008). The role of the innate immune system, including dendritic cells and airway epithelial cells, both of which may play roles in allergen recognition and the initial response of the body to those allergens, may also be highly important and a target for further therapeutic regimens (Lewkowich and Wills-Karp 2008).

In human studies, it has been shown that after an acute allergen exposure, there is an early asthmatic response (EAR) and then, 3–8 h later, a late asthmatic response (LAR). The LAR can be clinically more significant than the EAR (Cockcroft et al. 2007). Airway hyperresponsiveness to histamine and methacholine was found to be increased following allergen challenge, in some subjects long-lasting, showing that allergen exposure can cause bronchoconstriction in asthma; this was also associated with an increase in bronchoalveolar lavage eosinophilia (Cockcroft et al. 2007). Studies of allergen inhalational challenges, using sputum induction, have shown a greater eosinophilic and basophilic airway inflammatory presence in the LAR compared to the EAR, with basophils hitting their maximal level earlier than eosinophils (Cockcroft et al. 2007). Using allergen challenges can help to measure the effect new treatments under study have on the LAR, airway hyperresponsiveness, and influx of eosinophils.

Treatment of Allergic Asthma

Patient education is highly necessary in all aspects of asthma management, including allergen avoidance and/or treatment. Avoidance of allergens is highly recommended in a strategy for treatment and control of asthma. Multiple studies have

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shown benefit from dust mite controls (mattress and pillow encasements, reduction of indoor humidity, washing bedding in hot water, and removal of carpet) and cockroach control (Lugogo et al. 2010). Avoidance of living with pets is highly recommended for those who demonstrate sensitivity based on allergen testing. For those who are unable to do this, excluding the pet from the bedroom, removal of carpeting, frequent vacuuming of furniture and flooring, and use of room air filters may be helpful (Boulet 2008). Eradication of pests, such as mice, rats, and cockroaches, is also helpful. Studies have shown improvement in symptoms, medication needs, airway hyperresponsiveness, and exacerbations with reduced exposures to allergens in the home. It may take several weeks for the improvement in symptoms to become apparent (Liu et al. 2011). Avoidance of outdoor pollens and molds can be partially achieved by keeping windows closed in the home, using air conditioning when driving, and bathing prior to bed (to remove pollen and mold spores from hair and skin).

Treatment with antihistamines and nasal corticosteroids can help to abate the effect that allergens have on the asthmatic patient (Guilbert et al. 2008). This may occur via interactions of effector cells and cytokines. However, reduction of nasal congestion and blockage also leads to better air movement and thus improved humidifying and warming of the air, as well as filtering of allergens and particles, all of which help reduce irritants to the lower airways, reducing hyperresponsiveness (Liu et al. 2011).

Allergen immunotherapy, specific to the allergens to which the individual patient is allergic, can be helpful. However, due to the risks of reactions, including asthma attacks and anaphylaxis, it is generally recommended that patients whose asthma is not stable not be treated with this type of intervention. Allergen immunotherapy is a series of injections that need to be given over the course of several years; thus the time commitment, plus time involved in getting the injection and monitoring in the office after, is not an option for some patients.

Use of a monoclonal antibody to IgE, omalizumab, has been associated with improved asthma control and a decline in exacerbations (Lugogo et al. 2010). Some studies have also shown a decline in the amount of steroid required by patients to keep their asthma controlled. This is an expensive therapy, requiring an injection every 2–4 weeks, and has been associated with anaphylaxis in some patients. Dosage depends on the patient's weight and total IgE level. This has thus far been used primarily in severe patients not responding to more commonly used asthma therapies.

Occupational Asthma

Occupational asthma (OA) is caused in the workplace by either development of a sensitization to a workplace agent (OA with latency) or due to one or more acute inhalational incidents at work. The environmental exposure at work to a particular agent causes variable airflow limitation or hyperresponsiveness, with inflammation. This affects 10 % of adults with adult-onset asthma (Malo et al. 2008). Common high molecular weight (HMW) agents noted to cause OA with latency in the workplace include cereals, animal-derived allergens, enzymes, gums, latex, and seafoods. The HMW agents act as a complete antigen, to provoke a direct immune response. Common low molecular weight (LMW) agents noted to cause OA with latency include isocyanates, wood dusts, anhydrides, amines, fluxes, dyes, formaldehyde, acrylate, drugs, and metals. LMW agents act as haptens and need a human carrier molecule to combine with (such as albumin protein) to provoke an immune response. Patients who are atopic and smoke are at higher risk for development of OA (Malo et al. 2008).

OA should be suspected in new onset of asthma symptoms in a patient who complains symptoms are worse at work or the evening after work, with improvement on weekends or vacation. Coworkers with similar exposures may have similar symptoms. Use of agents noted in the above paragraph in the workplace should heighten suspicion. Rhinitis symptoms and/or atopy make OA more likely (Glazer and Pacheco 2008). A history of the current occupation and exposures, as well as previous, and

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hobbies is necessary. Contact with the workplace may be necessary to determine which exact chemical exposures are present. A history of nasal or eye symptoms preceding the onset of asthma symptoms is typical for HMW agents. Symptoms start while at work, or closely thereafter, and are not present on weekends or vacations, until OA has progressed to the point where symptoms are present at all times (Malo et al. 2008).

The differential diagnosis of OA includes vocal cord dysfunction (VCD), allergic rhinitis, and hypersensitivity pneumonitis. As these conditions are treated differently, firm diagnosis is important (Glazer and Pacheco 2008). Additionally, confirmation objectively is of high importance due to the social and financial impact OA can have if misdiagnosed or undiagnosed. Diagnosis may involve skin testing, bronchial challenge to histamine or methacholine, and bronchial challenges to the suspected agent. Monitoring of peak flows in a serial fashion, at and away from work, may assist in accurate diagnosis. Providing the correct diagnosis, and removal from the exposure or elimination of the exposure, can cause OA to completely remit in the majority of cases (Malo et al. 2008). Treatment with inhaled corticosteroids and other asthma treatments may be helpful in management of symptoms (Glazer and Pacheco 2008).

Cross-References

- ▶ Allergen Avoidance: Avoidance Strategies for Skin Allergies
- ▶ Allergen Avoidance: Cockroach and Rodent Avoidance
- ▶ Allergen Avoidance: Dust Mite Avoidance
- ▶ Allergen Avoidance: Fungi and Mold Avoidance
- ▶ Allergen Avoidance: Furry Animal Avoidance
- ▶ Allergen Avoidance: Pollen Avoidance - Tree, Grass, and Weed
- ▶ Immunotherapy for Asthma
- ▶ Immunomodulator Therapy of Asthma

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Asthma Variants: Cough-Variant Asthma

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Definition

Chronic cough is defined as a cough that is present for more than 8 weeks in adults (Desai and Brightling 2010) and 4 weeks in children (Rank et al. 2007). The differential diagnosis of chronic cough includes asthma, gastroesophageal reflux

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(GER), and postnasal drip, in addition to other less common causes (Chung and Widdicombe 2010). Cough-variant asthma is seen with a cough in isolation (no wheeze or sense of dyspnea or chest tightness) and is frequently nocturnal. This diagnosis can be confirmed with identifying reversible airflow limitation via spirometry or bronchial hyperresponsiveness via a bronchial methacholine or other similar challenge (Chung and Widdicombe 2010; Rank et al. 2007). Methacholine bronchial challenge has a high negative predictive value (100 %) in multiple studies (Rank et al. 2007). Physical exam and baseline spirometry are often normal; thus, bronchial challenge testing is often needed for a firm diagnosis (Desai and Brightling 2010).

Cough-variant asthma may be due to bronchial smooth muscle contractions, which can activate cough receptors via physical stimulus; thus, β-adrenergic bronchodilators can effectively calm the cough. Vagal nerve innervation due to inflammation along the bronchi may contribute (Rank et al. 2007).

Pathologically, sputum would show an eosinophilic predominance. Eosinophils are also prominent in bronchial biopsies, as well as a thickened basement membrane (Chung and Widdicombe 2010). However, these pathologic specimens are not needed for a firm diagnosis.

Treatment will usually need to be prolonged (at least 3 months), with an inhaled corticosteroid regularly and as-needed bronchodilators. A short trial of oral corticosteroids may be needed if inhaled steroids alone are not sufficient to control the cough (Chung and Widdicombe 2010). Cough suppressants are not recommended, as they do not treat the underlying cause of the cough.

If the cough is not improved with typical asthma treatments as discussed above, bronchial challenge testing must be done. If this is negative, pursuing other diagnoses in the differential diagnosis of chronic cough should be undertaken. Chronic rhinosinusitis, gastroesophageal reflux disease (GERD), medications (angiotensin-converting enzyme (ACE) inhibitors), and chronic eosinophilic bronchitis (Boulet 2008) can mimic cough-variant asthma. Rhinosinusitis can cause cough due to laryngeal irritation from postnasal drip. GER acid exposure from stomach contents can also irritate the throat, causing cough. Cough due the ACE-inhibitors typically resolves when the offending medication is stopped. Determining the real diagnosis and treatment is key for quality of life.

Prognosis for patients with cough-variant asthma is unclear. One study showed that 54 % of children with cough-variant asthma (diagnosed by positive methacholine bronchial challenge) went on to develop a more classic asthma (with recurrent attacks of shortness of breath with wheezing) during a follow-up period of at least 3 years (Todokoro et al. 2003). Further studies as to prognosis would be helpful in giving reasonable advice to patients regarding their prognosis.

Cross-References

- ▶ Diseases in DDx of Asthma: Alpha 1 AT Deficiency
- ▶ Diseases in DDx of Asthma: Bronchopulmonary Dysplasia
- ▶ Diseases in DDx of Asthma: COPD
- ▶ Diseases in DDx of Asthma: Croup
- ▶ Diseases in DDx of Asthma: Differential Diagnosis of Asthma
- ▶ Diseases in DDx of Asthma: Vocal Cord Dysfunction

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Atopic Dermatitis

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Synonyms

Atopic eczema; Chronic constitutional eczema; Prurigo Besnier

Definition

Atopic dermatitis is an inflammatory, chronic or chronically relapsing, noncontagious skin disease characterized by severe itching, scaling, and sometimes weeping red papules, plaques, and crusty excoriation.

Historical Background

Probably one of the first mentioned atopic patients was the Roman Emperor Augustus, who showed typical clinical symptoms of atopic dermatitis, bronchial asthma, and hay fever (Ring 2000). In the first textbook of dermatology "*De Morbis Cutaneis,*" the Italian physician Girolamo Mercuriale (1572) mentioned skin changes resembling atopic dermatitis. The first detailed description of atopic dermatitis was given in 1808 by the British physician Robert Willan. In 1892, the French physician Ernest Henri Besnier described an eczematous and intensely itching skin condition as *dermatitis multiformis pruriginosa* and first recognized the link to hay fever and allergic asthma. Then, between 1920 and 1930, the concept of atopic diseases including atopic dermatitis was introduced.

Epidemiology

Atopic dermatitis is a common chronic inflammatory skin disease. During early childhood, 10–15 % of the children suffer, at least temporarily, from atopic dermatitis. However, symptoms often become better with age, and while in adulthood, 70 % of patients who suffered from atopic eczema at young age are symptom-free, the prevalence is around 1.5–3 % in adults (Worm et al. 2006). Epidemiologic studies point to a further increase in the incidence of atopic dermatitis especially in developing countries (Asher et al. 2006).

Pathogenesis

The pathogenesis of atopic dermatitis is complex and multifactorial (Leung et al. 2004). Patients often show a disturbed epidermal skin barrier, which facilitates the loss of water as well as the penetration of allergens or pathogens, thus promoting skin dryness and inflammation, respectively. In addition, immune aberrations like enhanced synthesis of IgE antibodies against environmental factors are found. Studies point to a genetic background propagating these disturbances (Barnes 2010). Besides a familial enhanced occurrence, various genes important for the development of a well-structured epidermal barrier or the balanced regulation of the innate and acquired immune system have been identified, which disturbed expression predispose for the onset of atopic dermatitis (Bieber 2008). For example, mutations in the filaggrin gene, which expresses a protein important for forming a protective cornified layer and which degraded products serve as natural moisturizing factors (Kezic et al. 2008), have been shown to be associated with the risk of developing atopic dermatitis (Palmer et al. 2006).

Dependent on the presence of elevated IgE serum concentrations and skin test reactivity to allergens, affected individuals can be subgrouped into extrinsic or intrinsic atopic eczema patients. Allergens taken up by the impaired skin barrier might be bound by dendritic cells via IgE antibodies fixed to the high-affinity IgE receptor on these cells in patients suffering from extrinsic eczema (Bieber 2008). The dendritic cells will then uptake the allergen and process it for

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Atopic Dermatitis, Fig. 1 Baby with atopic dermatitis affecting the face, trunk, and extremities

presentation to T lymphocytes in the regional lymph nodes. Activated T cells differentiate into Th2 cells secreting cytokines like IL-4, IL-5, IL-9, IL-13, and IL-31. Besides promoting the differentiation of B cells into IgE-producing plasma cells, the Th2 cells are probably mainly involved in the elicitation of acute, pruritic dermatitis, while Th1 cells characterized by the synthesis of INF-γ are chiefly found in chronic eczematous lesions.

Clinical Manifestation

Acute lesions show itchy, erythematous, infiltrated, sometimes weeping, red papules and patches, which can be covered with yellowish crusts due to bacterial superinfection (Fig. 1). Chronic lesions are characterized by enhanced scaling and coarsening of the skin relief, called lichenification. In adults, the pruritic variant of atopic eczema could also present with severely itching nodules and plaques. While in neonates and children up to 2 years of age, skin lesions are mostly localized to the scalp, face, trunk, and extensor surfaces of the extremities (Fig. 2); later, the flexural areas, hands, neck, face, and eyelids are mostly affected.

Patients report that the often extreme itch, particularly at night, is the most stressful symptom, severely affecting daily activities and the quality of life. In addition, scratching leading to excoriations further increases the irritation and inflammation of the skin, thus leading to a vicious circle.

Atopic Dermatitis, Fig. 2 Atopic dermatitis infected by *Staphylococcus aureus*, showing the typical yellowish plaques

Minimal variants of atopic dermatitis display tiny vesicles at the fingertips or toes (pulpitis sicca) (Fig. 3); dry, scaling lips (cheilitis); lacerations of the labial angle; eczema of the nipple lacerations at the ear lobes (fissures); bright, slightly scaly patches of the skin (pityriasis alba); and fine scales of the palms and soles (dyshidrotic eczema).

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Atopic Dermatitis, Fig. 3 Pulpitis sicca, characterized by superficial fissures covered with fine scales

A wide variety of potential trigger factors can cause disease exacerbations, including allergens, microbes, and irritants. Children can develop food allergies against milk, egg, or wheat, while adults rather show allergic reactions to aeroallergens like pollen, house dust mites, and animal dander, which sometimes can result in dermatitis on air-exposed body regions (eyelids, head-neck-shoulder-dermatitis). Both systemic (like a common cold) and cutaneous infections, caused by staphylococcus aureus or herpes simplex virus, can provoke eczematous lesions (Baker 2006). The same holds true for irritants such as textiles rubbing on the skin or promoting increased sweating. In addition, climate factors like low temperatures and low humidity as experienced during winter or negative and positive stress situations may promote relapses of atopic dermatitis.

Complications

Patients with atopic dermatitis are prone to develop various skin infections. These include impetiginization due to infection with *Staphylococcus aureus* (Miajlovic et al. 2010) (Fig. 1) eczema herpeticum caused by herpes simplex virus (characterized by disseminated painful blisters and erosions, often accompanied by fever and lymphadenopathy) the development of mollusca contagiosa and verrucae vulgaris, and increased colonization by *Pityrosporum ovale*, a fungal species evoking fine-scaling patches (Baker 2006).

Diagnosis

Diagnosis is based on clinical parameters, classified into major and minor criteria (Hanifin and Rajka 1980). Major features include the presence of chronically relapsing skin lesions in a typical distribution, itching, and a history of atopic diseases. Minor features are so-called atopic stigmata like dry skin (xerosis), thinning of the lateral part of the eyebrow (Hertoghe sign), or a doubled eyelid crease (Dennie-Morgan fold). Individual trigger factors should be identified. For allergens, this includes testing (determination of allergen-specific IgE, skin prick, and/or patch testing based on personal history).

Therapy

The therapeutic management should be adapted to the severity, the acuteness, and the course of the eczema, which can be classified into 4 levels.

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At level 1 (dry skin), the focus lies on both intense skin rehydration using ceramide or urea-based moisturizers and avoidance and reduction of trigger factors. At level 2 (mild eczema), topical antiseptics (e.g., triclosan, chlorhexidine in adequate ointments), itch-reducing measures such as oral antihistamines and topical corticosteroids of mild to moderate potency, or topical calcineurin inhibitors (tacrolimus, pimecrolimus) are added. UV therapy may be performed in patients older than 12 years. At level 3 (moderate eczema), topical steroids should be substituted by more potent corticosteroids, and at level 4 (severe persistent and/or generalized eczema), the potency of topical corticosteroids should be further increased if possible. In addition, systemically immunosuppressive treatment such as cyclosporine or short-term oral corticosteroid therapy may be performed.

After clearing of eczematous lesions, a proactive treatment should be considered for at least 3 months to stabilize the skin barrier and reduce the frequency of rebounds. This can be achieved by topical treatment with low-dose corticosteroids or calcineurin inhibitors twice a week on the initially affected skin areas. Daily basic skin care should be continued.

Cross-References

- ▶ Analytes and Biomarkers: IgE
- ▶ Cow's Milk Allergy
- ▶ Diagnostic Components: T Helper Cell Cytokines (IL-4, IL-5, IL-9, IL-10, IL-13, IL-17)
- ▶ Diagnostic Terms: Atopy
- ▶ Egg Allergy
- ▶ Food Allergens
- ▶ Food Allergy, Overview
- ▶ Genetic Regulation of IgE
- ▶ IgE Testing
- ▶ Induction of IgE Synthesis: Cellular Interactions and Molecular Events
- ▶ Role of IgE in Disease
- ▶ Topical Corticosteroids
- ▶ Topical Preparations: Calcineurin Inhibitors

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Autoimmune Lung Disease

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Synonyms

Collagen vascular disease-associated lung disease; Connective tissue disease-associated lung disease

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Definition

"Autoimmune lung disease" can be defined as representing a variety of respiratory disorders associated with the systemic connective tissue diseases.

Introduction

Autoimmune lung disease refers to the variety of respiratory disorders associated with the systemic connective tissue diseases. The designation *connective tissue disease* (CTD) is applied to the spectrum of systemic autoimmune diseases characterized by autoimmune phenomena and autoimmune-mediated organ damage. Although grouped together, there is significant heterogeneity of clinical features associated with each specific CTD. The specific CTDs include rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), systemic sclerosis (SSc, scleroderma), poly-/dermatomyositis (PM/DM), Sjögren's syndrome (SjS), and mixed CTD (MCTD). Autoimmune-mediated lung injury is frequently identified in patients with CTD. There are numerous pulmonary manifestations associated with the CTDs, and essentially every component of the respiratory tract is at risk. Furthermore, certain CTDs are associated with specific types of lung disease (Tables 1 and 2) (Frankel and Brown 2006; Olson and Brown 2009; Olson et al. 2012). Although many of these lung manifestations occur within the first few years of the CTD diagnosis, their development much later on is not unusual, and they may even be the presenting feature of an underlying CTD. In this entry, an overview of the categories of lung disease encountered in patients with CTD is provided followed by a brief review of the lung manifestations associated with the specific CTDs.

Autoimmune Lung Disease, Table 1 Primary and secondary pulmonary manifestations of connective tissue diseases (Olson et al. 2012)

Primary manifestations
Pleural
Pleurisy
Effusion/thickening
Airways
Upper
Cricoarytenoid disease
Tracheal disease
Lower
Bronchiectasis
Bronchiolitis
Vascular
Pulmonary arterial hypertension
Vasculitis
Parenchymal
Interstitial lung disease
Diffuse alveolar hemorrhage
Acute pneumonitis
Rheumatoid nodules
Secondary manifestations
Infections
Drug toxicity
Malignancy
Thromboembolism

Autoimmune Lung Disease, Table 2 Most common CTD-associated pulmonary manifestations

	SSc	RA	Sjögren's	MCTD	PM/DM	SLE
Airways	–	++	++	+	–	+
ILD	+++	++	++	++	+++	+
Pleural	–	++	+	+	–	+++
Vascular	+++	–	+	++	+	+
DAH	–	–	–	–	–	++

SSc systemic sclerosis, *RA* rheumatoid arthritis, *CTD* connective tissue disease, *MCTD* mixed connective tissue disease, *PM/DM* polymyositis/dermatomyositis, *SLE* systemic lupus erythematosus, *ILD* interstitial lung disease, *DAH* diffuse alveolar hemorrhage. The number of + signs indicates relative prevalence of each manifestation

Categories of Lung Involvement

When a patient with CTD presents with respiratory symptomatology, a number of diagnostic possibilities should be considered: infection, drug-induced lung toxicity, direct pulmonary complications (e.g., interstitial lung disease [ILD]), indirect complications (e.g., respiratory muscle weakness), and cardiovascular complications (e.g., cardiac ischemia, cardiomyopathy) (Olson and Brown 2009) (Table 1).

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Respiratory Infection

Respiratory infections are a frequent finding in patients with CTD and account for significant morbidity and mortality. Specific risk factors that may predispose CTD patients to develop respiratory infections include the use of immunosuppressive therapies, the presence of respiratory muscle weakness or intrinsic lung disease, and the presence of underlying immune dysfunction. As a result, thorough evaluation to exclude the presence of routine or opportunistic infections should be undertaken in any CTD patient with respiratory symptomatology.

Medication-Induced Lung Toxicity

Many of the anti-inflammatory and immunosuppressive medications used to treat CTD are associated with lung toxicity. These include aspirin, nonsteroidal anti-inflammatory drugs, sulfasalazine, methotrexate (MTX), cyclophosphamide, azathioprine, mycophenolate mofetil, leflunomide, and the anti-TNF-alpha antagonists (Olson and Brown 2009). However, because the clinical presentation is often nonspecific and can mimic intrinsic lung disease associated with CTD, a diagnosis of drug-induced lung disease can be challenging.

Of all the immunosuppressive medications used to treat patients with CTD, MTX is generally considered to have the most potential for pulmonary toxicity. Symptomatically it is characterized by the subacute onset of dyspnea, cough, and fever. However, more acute, chronic, or even delayed reactions have been described. Radiographically, a pattern of nonspecific infiltrates in the lower lung fields may be present, while the histopathologic patterns seen on surgical lung biopsy often include a lymphoplasmacytic infiltrate with or without granulomata, along with acute and organizing diffuse alveolar damage (DAD). Neither the duration nor the dose predicts MTX lung toxicity, though underlying RA and male gender may be risk factors to its development (Olson and Brown 2009; Olson et al. 2012). Treatment for MTX-associated pneumonitis includes the discontinuation of MTX and the initiation of corticosteroids. Mortality associated with MTX pneumonitis can be as high as 13–22 % (Olson and Brown 2009; Olson et al. 2012).

Over the past 15 years, the management of the rheumatic diseases has been revolutionized by the advent of targeted biologic therapy (e.g., anti-TNF-α antagonists, B and T cell blockers, and interleukin antagonists). There have been case reports describing the development of diffuse lung disease in patients being treated with some of these agents suggesting a component of direct pulmonary toxicity associated with their use (Olson and Brown 2009; Olson et al. 2012). However, even more significant than their potential for lung toxicity, it is important to recognize that biologic therapies are highly immunosuppressive and patients treated with these medications are at particularly high risk for both typical and atypical respiratory infections.

Indirect Respiratory Complications

By definition, the CTDs are systemic in nature, and as such, virtually all organ systems are impacted. Indirect respiratory complications of underlying CTD may include musculoskeletal abnormalities (e.g., respiratory muscle weakness), gastrointestinal diseases (e.g., gastroesophageal reflux or aspiration), immunologic dysfunction, hematologic (e.g., autoimmune hemolytic anemia), cardiovascular (e.g., cardiomyopathy), or vascular (e.g., thromboembolism or pulmonary arterial hypertension [PAH]). Abnormalities in one or more of these systems often lead to respiratory compromise even in the absence of underlying intrinsic lung disease and highlight the need for a comprehensive, often multidisciplinary, assessment of the CTD patient with respiratory symptoms (Olson and Brown 2009).

Intrinsic Lung Manifestations

Each of the unique anatomic compartments of the lung can be involved by one or more pathologic processes that adversely affect its ability to function normally. The airway, from the larynx to the bronchiole; the parenchyma; the vasculature; and the pleura can all be involved either individually or in some combination (Frankel and Brown 2006; Olson and Brown 2009) (Table 2).

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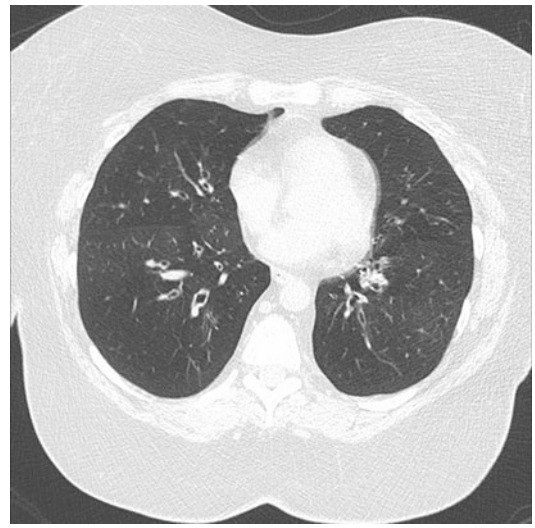
For example, ILD is frequently identified in preexisting CTD. In fact, recent studies have shown that radiographic prevalence rates of subclinical ILD in select CTD cohorts may be as high as 33–57 % (Doyle et al. 2012). ILD is particularly common in patients that have SSc, PM/DM, or RA. However, just because ILD is identified in a CTD patient does not mean the two are necessarily related. The presence of preexisting RA does not preclude, and may in fact predispose toward, the development of lung injury due to other causes (e.g., infection or medication-induced pneumonitis). In this regard, just as with any other patient found to have ILD, a comprehensive, multidisciplinary evaluation is needed to explore all potential etiologies (e.g., infection, drug toxicity, environmental and occupational exposures, familial disease, smoking-related lung disease, and malignancy). Determining whether the ILD is associated with the underlying CTD is often decided through a process of elimination.



Autoimmune Lung Disease, Fig. 1 Computed tomography image of bronchiectasis in a patient with rheumatoid arthritis

Pulmonary Manifestations Associated with Specific CTDs

Rheumatoid Arthritis (RA)

RA is the most common CTD and affects approximately 1 % of the population worldwide. Pulmonary complications are common, may be the presenting manifestation of the disease, can impact every component of the respiratory tract, and account for 10–20 % of deaths (Olson and Brown 2009; Olson et al. 2011; Olson et al. 2012). Airways disease is particularly common in RA. The cricoarytenoid joint is affected in the majority of patients. The clinical importance of mild laryngoscopic changes is of uncertain significance; however, true cricoarytenoid arthritis can lead to life-threatening airway compromise – particularly in the setting of endotracheal intubation (Olson and Brown 2009). Bronchiectasis has been noted in up to 58 % of patients (Olson and Brown 2009; Olson et al. 2012), is more common in long-standing RA, and predisposes the patient to severe respiratory infection (Fig. 1). Bronchiolitis is common as well, and physiologic evidence of its presence occurs in nearly half of patients (Olson and Brown 2009; Olson et al. 2012). On surgical lung biopsy a cellular or fibrosing bronchiolar process is typically identified (Hayakawa et al. 1996). Cellular bronchiolar diseases include follicular bronchiolitis (more commonly) and rarely diffuse panbronchiolitis. Fibrosing bronchiolar disease, termed obliterative bronchiolitis or constrictive bronchiolitis, is poorly responsive to immunomodulatory therapy and frequently leads to respiratory failure and death (Olson and Brown 2009; Olson et al. 2012).

Pleuritis and pleural effusions are common in men with established disease, high rheumatoid factor (RF) titers, and rheumatoid nodules (Olson and Brown 2009). Asymptomatic pleural effusion may be present in as many as 70 % of patients, while symptomatic effusions occur in approximately 5 % (Olson and Brown 2009). Because a number of other pleural diseases can occur in RA, including infection/empyema, sterile empyema, chylothorax, and malignancy, the etiology of an unidentified effusion should be pursued. Biochemical characteristics of RA pleural effusions include an exudative process, a low pH (< 7.3), a decreased glucose level

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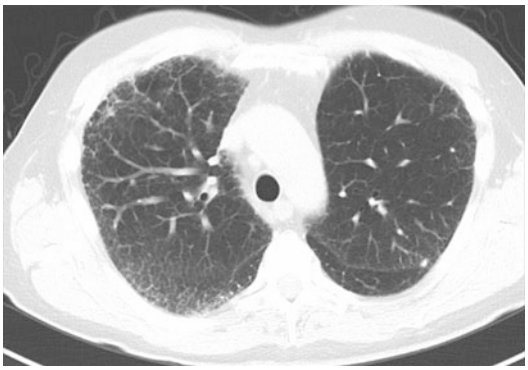
(< 50 % of the serum glucose level), an elevated LDH (> 700 IU/L), and an elevated RF titer (Olson 2009).

Rheumatoid nodules are present in as many as 20 % of RA patients by high-resolution computed tomography (HRCT) imaging and are the most common finding on surgical lung pathology occurring in as high as 33 % of specimens (Olson and Brown 2009; Olson et al. 2012). Multiple nodules may be present, and central cavitation occurs in approximately 50 % of these lesions (Olson and Brown 2009; Olson et al. 2012). Histopathologically, these nodules comprise central fibrinoid necrosis with surrounding granulomatous inflammation. Although most often asymptomatic, rheumatoid nodules can result in symptoms secondary to complications (including pneumothorax and hemoptysis) and must be distinguished from infection or malignancy (Olson and Brown 2009; Olson et al. 2012).

ILD may be seen in more than 50 % of all patients with RA (Olson and Brown 2009; Doyle et al. 2012). However, clinically significant disease is much less common. Unlike articular RA which is more common in women, RA-ILD appears to be more common in men. Although the nonspecific interstitial pneumonia (NSIP) pattern of lung injury is the most common pattern encountered among CTDs as a whole (Park et al. 2007), in RA, usual interstitial pneumonia (UIP) appears to be the most common pattern (Lee et al. 2005; Park et al. 2007; Kim et al. 2010) (Fig. 2). A recent study has highlighted that ILD may be the first clinically apparent manifestation of RA and that patients without arthritis but with a positive anti-cyclic citrullinated peptide (CCP) antibody and airways disease or ILD may represent a pre-articular RA phenotype (Fischer et al. 2012b). Eosinophilic pneumonia has also been reported in patients with RA.

Systemic Lupus Erythematosus (SLE)

Some form of lung abnormality occurs in nearly all patients with SLE (Swigris et al. 2008; Olson 2009). Pleuritis is the most common pulmonary manifestation of SLE. Pleuritic chest pain occurs in 35–60 % of patients during the course of disease and may be the presenting manifestation as well. Clinically evident pleural effusions are identified in nearly half of patients with pleurisy. Autopsy studies report pleural involvement in almost all and pleural effusions in approximately two-thirds of subjects. Pleural effusions are likely to be bilateral, small to moderate in size, and exudative. A diagnostic evaluation is indicated when a new effusion is seen as other etiologies must be excluded including infection (parapneumonic effusions/empyema), pulmonary embolism, and congestive heart failure. Symptomatic pleurisy typically responds to nonsteroidal anti-inflammatory agents, and more severe disease may require immunosuppressive therapy (Swigris et al. 2008; Olson et al. 2011).



Autoimmune Lung Disease, Fig. 2 Computed tomography image of a lung injury pattern suggestive of usual interstitial pneumonia in a patient with rheumatoid arthritis

Pulmonary hypertension may be the result of a primary vascular abnormality with histopathologic features similar to those in idiopathic PAH or SSc-PAH or as a result of a variety of cardiopulmonary disorders including ILD, thromboembolic disease, Libman-Sacks endocarditis, cardiomyopathy, diastolic dysfunction, or obstructive sleep apnea (Olson and Brown 2009; Olson et al. 2012).

Antiphospholipid antibodies (aPL) are common in SLE, occurring in approximately one-third of patients. Their presence is associated with an increased risk of thromboembolism and fetal loss. In addition to the thrombotic

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complications of disease including pulmonary emboli, aPL has been associated with PAH, diffuse alveolar hemorrhage (DAH), and DAD (Asherson et al. 2006).

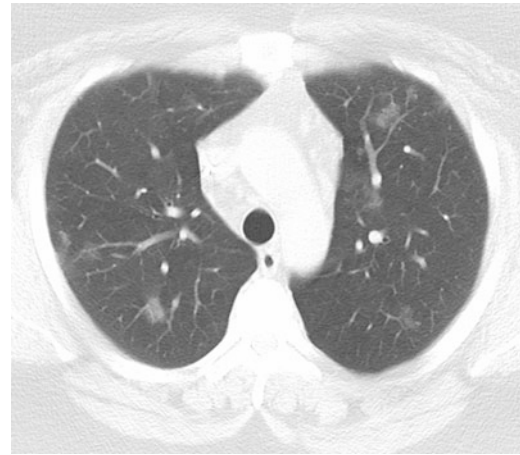
Clinically significant airways disease is rare in SLE. Similarly, clinically significant ILD is less common in SLE than in the other CTDs. Like other forms of CTD-associated ILD, the histologic patterns of SLE-associated ILD mirror the patterns described for the idiopathic interstitial pneumonias, most commonly NSIP (Bertoli et al. 2007; Park et al. 2007).

DAH is a life-threatening pleuropulmonary manifestation of SLE. At presentation, symptoms include the acute onset of dyspnea and cough, imaging studies may reveal alveolar infiltrates (Fig. 3), and laboratory data may confirm a declining hematocrit. The absence of hemoptysis does not necessarily exclude the diagnosis. Furthermore, the presence of hemoptysis in a patient with SLE does not always imply a diagnosis of DAH as it can occur in both pulmonary infections and acute lupus pneumonitis (discussed below). The diagnosis can be confirmed with sequential bronchoalveolar lavage samples revealing an increasing red blood cell count.

The clinical characteristics of acute lupus pneumonitis include the acute onset of fever, dyspnea/tachypnea, cough, and hypoxemia with radiographic evidence of bilateral patchy or diffuse infiltrates, typically with a basilar predominance and often resulting in acute respiratory failure (Swigris et al. 2008; Olson and Brown 2009). The most frequent histologic pattern is DAD although some have described the presence of capillaritis. There has been debate about whether acute lupus pneumonitis is a distinct syndrome or whether it is actually representative of either DAH (with or without capillaritis), DAD, or acute respiratory distress syndrome resulting from a specific etiology (e.g., infection) (Swigris et al. 2008; Olson and Brown 2009).

Shrinking lung syndrome (SLS) is a rare complication of SLE that results in unexplained dyspnea and restrictive physiology with low lung volumes in the absence of significant underlying pleuroparenchymal disease (Toya and Tzelepis 2009) (Fig. 4). Although the etiology of SLS is unknown, theories regarding its pathogenesis speculate about diaphragmatic dysfunction either due to neuromuscular myopathy with respiratory muscle weakness or diminished diaphragmatic excursion due to chronic pleural inflammation. The prognosis is favorable as most patients either improve or stabilize with therapy.

Patients with SLE are also at risk for developing the syndrome of acute reversible hypoxemia.



Autoimmune Lung Disease, Fig. 3 Computed tomography image of alveolar infiltrates suggestive of diffuse alveolar hemorrhage in a patient with systemic lupus erythematosus

Autoimmune Lung Disease, Fig. 4 Computed tomography image of shrinking lung syndrome in a patient with systemic lupus erythematosus

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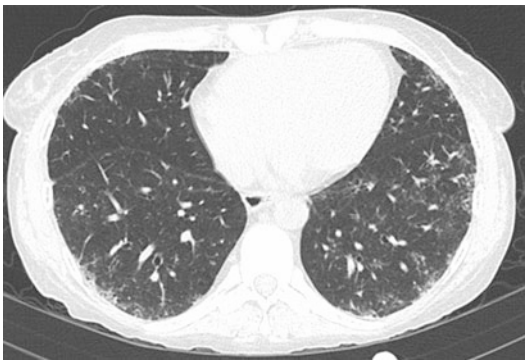
These patients present with the acute onset of hypoxemia and a widened alveolar-arterial gradient on arterial blood gas assessment and have normal radiographic imaging studies. The pathophysiology of this syndrome is unknown. A rapid and dramatic response to glucocorticoids is a characteristic finding in patients with acute reversible hypoxemia (Swigris et al. 2008; Olson and Brown 2009).

Systemic Sclerosis (SSc)

SSc is a systemic autoimmune disease characterized by autoimmunity, fibrosis, and small vessel vasculopathy. Intrinsic lung disease is identified in most patients with SSc; indeed, ILD and PAH are its leading causes of mortality (Steen 2005). The true prevalence of PAH in SSc is unknown, but it is estimated that right-heart catheter proven PAH has a prevalence of approximately 10 % (Fischer et al. 2012a). Risk factors for the development of SSc-PAH include limited skin involvement, long-standing Raynaud's phenomenon, extensive cutaneous telangiectasia, positive anti-centromere antibody, positive "isolated" nucleolar ANA, or isolated reduction in diffusing capacity for carbon monoxide (Fischer et al. 2012a). ILD is identified more often in SSc than with any other CTD; evidence of radiographic findings of ILD occurs in nearly all patients with SSc, and clinically significant disease occurs in approximately 40 % (Steen 2005; Olson and Brown 2009; Olson et al. 2012). The most prevalent histologic pattern identified in SSc is fibrotic NSIP followed by the UIP lung injury pattern (Bouros et al. 2002; Park et al. 2007) (Fig. 5).

Clinically significant airways disease appears to be relatively rare in SSc. Subtle airway abnormalities may be related to prior tobacco exposure or possible subclinical follicular bronchiolitis (Olson and Brown 2009; Olson et al. 2012). Unlike RA or SLE, symptomatic pleuritis and/or pleural effusions are uncommon in SSc. Esophageal dysmotility and gastroesophageal reflux disease are quite common in SSc, and most SSc patients require chronic proton-pump inhibitor therapy. Finally, there appears to be an increased risk of bronchogenic carcinoma associated with SSc (Olson and Brown 2009; Olson et al. 2012).



Autoimmune Lung Disease, Fig. 5 Computed tomography image of a lung injury pattern suggestive of nonspecific interstitial pneumonia in a patient with systemic sclerosis

Mixed Connective Tissue Disease (MCTD)

MCTD often resembles either SSc or SLE. It is characterized clinically by SLE or SSc-type symptoms but is distinguished from these and other CTDs by its serologic profile of a positive ANA along with an isolated positive anti-RNP antibody. MCTD is often associated with similar pulmonary manifestations as SSc, and these patients are thus incorporated into the "scleroderma spectrum" of disease. Practically speaking, because MCTD patients have similar pulmonary manifestations as SSc, heightened surveillance for clinically significant ILD and annual PAH screening is recommended (Fischer et al. 2012a).

Polymyositis/Dermatomyositis (PM/DM)

Both PM and DM are characterized by inflammatory muscle disease involving the proximal muscle groups. DM is further defined by its characteristic cutaneous involvement. Some form of pulmonary involvement occurs in over 50 % of patients, and ILD is the most common and potentially most devastating pulmonary manifestation of PM/DM (Schwarz 1998; Olson and Brown 2009). "Anti-synthetase syndrome" is a subtype of PM/DM and is characterized by a combination of inflammatory myopathy, ILD,

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fever, inflammatory arthritis, Raynaud's phenomenon, "mechanic's hands," esophageal dysmotility, and the presence of an anti-tRNA-synthetase antibody (e.g., anti-Jo-1, anti-PL-7, anti-PL-12) (Fischer et al. 2009; Solomon et al. 2011). Many patients with anti-synthetase syndrome have an incomplete presentation of the condition, and inflammatory muscle disease may be absent or subclinical in nature (Fischer et al. 2009; Solomon et al. 2011).

ILD is the most common pulmonary manifestation of PM/DM, and its presence has been associated with increased morbidity and mortality (Schwarz 1998). Clinically significant disease appears to occur in approximately 30 %, whereas HRCT evidence of ILD may be present in over 70 % of patients with PM/DM (Schwarz 1998; Olson and Brown 2009; Olson et al. 2012). ILD may be the presenting manifestation in many patients and is particularly common in those with anti-synthetase syndrome (Solomon et al. 2011). NSIP is the most common pattern seen on surgical lung biopsy followed by UIP and organizing pneumonia (Douglas et al. 2001; Arakawa et al. 2003). An acute interstitial pneumonia-like disease occurs with an underlying histopathologic pattern of DAD. The ILD encountered with anti-synthetase syndrome often has a characteristic HRCT pattern suggesting NSIP with overlapping organizing pneumonia with extreme bibasilar predominance and reticular and ground-glass opacifications that appear hug or "pancake" the diaphragm (Fischer et al. 2009) (Fig. 6).

Similar to SSc, esophageal dysmotility and gastroesophageal reflux disease are quite common in PM/DM. Medication therapy with proton-pump inhibitors for gastroesophageal reflux disease and a proactive approach to prevent aspiration are usually advised. Airways, pleural, and pulmonary vascular diseases are rare in PM/DM (Schwarz 1998).

Sjögren's Syndrome (SjS)

SjS is a systemic autoimmune disorder characterized by lymphocytic infiltration of the exocrine glands. The salivary and lacrimal glands are most often involved leading to the characteristic symptoms of disease including dry eyes (keratoconjunctivitis sicca) and dry mouth (xerostomia). Small airways disease is the most common pulmonary abnormality, occurring in more than half of patients with SjS (Olson and Brown 2009). In these patients, pulmonary physiologic abnormalities are typically mild and tend to remain stable over time. Histopathology studies of lung tissue from SjS patients with more severe obstructive lung disease have revealed evidence of lymphocytic or follicular bronchiolitis (Deheinzelin et al. 1996; Ito et al. 2005).

Autoimmune Lung Disease, Fig. 6 Computed tomography image of a pattern suggestive of nonspecific interstitial pneumonia with overlapping organizing pneumonia. Note the extreme bibasilar predominance

Pleural and pulmonary vascular disease complications are quite rare in patients with primary SjS, and their presence should highlight the need for evaluation of alternative etiologies. Clinically significant ILD is estimated to occur in 8–38 % of SjS patients (Papathanasiou et al. 1986; Olson and Brown 2009). A higher proportion of patients have subclinical ILD (Doyle et al. 2012). The most common histopathologic pattern identified in SjS is NSIP, but it is not uncommon to find other lung injury patterns, and lymphocytic interstitial pneumonia in particular (Fig. 7), in patients with SjS (Deheinzelin et al. 1996; Lee et al. 2005; Parambil et al. 2006).

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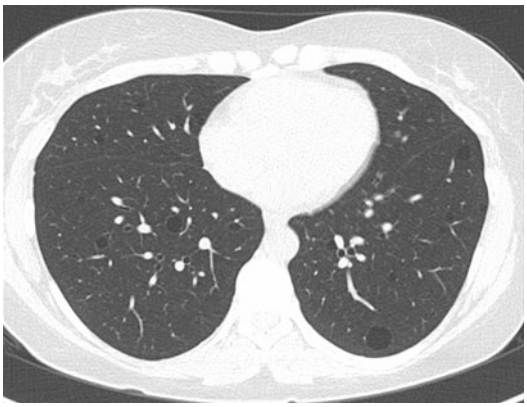

Autoimmune Lung Disease, Fig. 7 Computed tomography image of a pattern suggestive of lymphocytic interstitial pneumonia in a patient with Sjögren's syndrome. Note the presence of few small scattered cysts throughout the lung parenchyma

Conclusion

The CTDs represent a heterogeneous spectrum of systemic autoimmune diseases, and the lungs are a frequent target of autoimmune-mediated organ damage. Any of the lung compartments are at risk of injury, and multi-compartment lung involvement is a frequent finding. Consideration of extrinsic factors – such as respiratory infection and drug toxicity – as well as intrinsic lung manifestations needs to be considered in the CTD patient with respiratory symptoms. Because the intersection of lung disease and CTD is so complex, comprehensive assessment and multidisciplinary approaches to care are often needed to optimize the care of these patients. Each CTD has its own array of lung manifestations, and providers involved in the care of CTD patients should remain vigilant about assessing for a large variety of respiratory abnormalities.

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B

Basophils

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Synonyms

Basophil granulocytes

Definition

Basophils are the least common granulocyte (relative to neutrophils and eosinophils), are derived from bone marrow, and represent <1 % of the major leukocytes (or white blood cells) circulating in blood. They are named from the fact that their cytoplasmic granules stain with basic dyes (e.g., Alcian blue), as a result of their chondroitin sulfate-rich glycosaminoglycan content.

Historical Background

Human basophils were first described in 1878 by Paul Ehrlich, but only recently has greater insight surrounding their biology been attained (Schroeder 2011). In the late 1960s, basophils, like their tissue counterpart mast cells, were shown to store preformed histamine – a chemical responsible for some of the symptoms encountered during allergic reactions. It was later determined that allergens trigger histamine release from basophils (and mast cells) by interacting with specific IgE immunoglobulin bound to high-affinity receptors (FcεRI) expressed on both cell types. Recent findings from mouse models indicate that basophils play a natural role in mediating host immunity to helminthic parasites (Voehringer 2011) and possibly to ectoparasites (e.g., ticks) (Wada et al. 2010).

Functional Responses

Upon IgE/FcεRI cross-linking, a complex cascade of intracellular signals are initiated culminating in the release of inflammatory mediators and cytokine secretion. In addition to preformed histamine, basophils secrete de novo two other classes of mediators that are hallmark in allergic disease, leukotrienes (LT) and cytokines. LTC4 is rapidly generated from the sequential metabolism of phospholipid and arachidonic acid and secreted within minutes following activation. In regard to cytokines, basophils are now recognized as an important source of IL-4, a cytokine best known for its role in promoting IgE synthesis and in the polarization of T-helper cells

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toward the Th2 phenotype. The concept of basophils mediating a key role in allergic disease is further strengthen by their ability to secrete copious amounts of IL-13 (another important Th2 cytokine), as well as IL-3, IL-8, VEGF, and MIP-1α. Basophils typically secrete these cytokines over a span of hours rather than minutes. In addition, several IgE-independent innate immune stimuli (e.g., f-met peptide, C5a) are known to induce mediator release from basophils, but appear less capable of inducing cytokine secretion. Most all functional responses, both IgE dependent and IgE independent, are augmented by IL-3, and they are mediated by this cytokine binding to receptors (CD123) highly expressed on basophils. Basophils themselves have been shown to produce IL-3 following IgE-dependent stimulation, with this cytokine acting in an autocrine fashion to prime the cells for greater responsiveness.

Immunophenotypic Markers

Human basophils have been phenotyped for a wide variety of immunomodulatory cell surface determinants and are clearly positive for many key markers (FcεRI, CD32, CD123, CD116, CD125, CD126, IFN-αR2, Trk A, TLR1,TLR2, TLR4, TLR6) and unique markers (2D7, BB1, CD203c) (Kepley et al. 1995; McEuen et al. 1999; Buhring et al. 2001) while generally negative for many common markers (CD64, CD23, HLA-DR, $CD16^-$, CD2, CD3, CD122, CD19, CD20, CD114) (Schroeder 2011; Toba et al. 1999). Increased expression of CD203c, CD63, and, in some instances, CD69 is widely used in assessing basophil activation.

Basophils in Human Disease

The fact that basophils release three of the most relevant mediators in allergic inflammation alone points to these cells playing a critical role in the pathogenesis of human allergic disease. Yet direct evidence to support this concept remains to be fully elucidated. It is known that basophils selectively migrate from the blood into tissue sites during allergic inflammation. This has been demonstrated both in natural disease (e.g., lung of asthmatics) (Kepley et al. 2001; Ito et al. 2011) and also following experimental allergen challenge in models involving the skin, nose, and lung (Schroeder 2009). Symptoms associated with the so-called late-phase response (LPR), which occur ∼4–24 h after the early-phase response (a mast cell-mediated reaction), coincide with the appearance of basophils infiltrating the lesion site. Evidence of cytokine production (e.g., IL-4) by these infiltrating basophils further suggests immunomodulatory roles.

There is a long-held belief that basophil hyperresponsiveness in vitro is clinically predictive of one's allergic disease status. This is perhaps best evident among pediatric subjects with food allergy whereby the basophils from ∼80 % of these individuals spontaneously release histamine (and IL-4) in vitro (May 1976). In general, basophils from allergic individuals are more responsive (with regard to mediator release) to many diverse stimuli. Basophils from allergic individuals also tend to produce higher levels of IL-13 in response to IL-3 than do cells from nonallergic subjects. As a result of these observations, basophils are increasingly being used as "indicator" cells for conducting in vitro assays testing pharmacologic agents as well as in assessing the clinical efficacy of novel and existing therapies (Frischmeyer-Guerrerio and Schroeder 2012). For example, decreases in basophil responses are commonly investigated during allergen immunotherapy protocols, both standard and novel forms, to help assess clinical efficacy. Likewise, basophil responsiveness is often monitored during more novel therapies, such as those involving the use of anti-IgE (or omalizumab), since neutralization of serum IgE rapidly and markedly decreases FcεRI expression on these cells as well as responses to allergen (Saini and MacGlashan 2012).

While basophils are best known for their association with allergic inflammation, there is a body of evidence showing the involvement of

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these cells in specific delayed-type hypersensitivities, such as those associated with allergic contact dermatitis (e.g., exposure to poison ivy) (Mahapatro and Mahapatro 1984). Like late-phase responses to allergens, basophils have been shown to selectively infiltrate these lesion sites, but generally at much later time points (~3–7d). Additional studies are required to fully discern whether basophils are functionally active in these reactions. These reactions are thought to be T and/or B cell mediated, implying that basophil involvement in these reactions seems dependent, in part, by the actions of lymphocytes.

In Vivo Studies with Mouse Basophils

Analyses of ultrastructural components viewed in electron micrographs were the first to report evidence of a mouse equivalent of the human basophil (Dvorak 2000). While there remain significant phenotypic and functional inconsistencies between human and mouse basophils (Lee and McGarry 2007), studies investigating cells from genetically altered mice are beginning to support the concept that basophils play a direct role in allergic inflammation (Sokol et al. 2008), helminth infections (Voehringer 2011), and delayed-type hypersensitivity reactions (Ohnmacht et al. 2010). Importantly, these studies have confirmed evidence originating in humans that basophils do indeed secrete copious amounts of IL-4 (and IL-13). This capability to produce IL-4 has further prompted recent, but controversial, work in mice suggesting a role for basophils as IL-4-producing professional antigen-presenting cells (APC) that express MHC class II molecules capable of initiating the Th2 responses central to both allergic disease and helminth infections (Nakanishi 2010; Hammad et al. 2010). With the increasing capacity to selectively deplete basophils in vivo, such studies should soon provide evidence regarding the function of these cells in normal physiology as well as in immunopathology. The clinical relevance of such findings will then ultimately require translation to the human system for confirmation.

Cross-References

- ▶ Diagnostic Components: T Helper Cell Cytokines (IL-4, IL-5, IL-9, IL-10, IL-13, IL-17)
- ▶ Food Allergies, Diagnostic Testing
- ▶ IgE Receptor
- ▶ IgE Testing

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Biphasic, Protracted, and Late-Phase Reactions in Anaphylaxis

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Synonyms

Anaphylactic reaction; Anaphylactic shock; Anaphylactoid reaction; Life-threatening allergy

Definition

The signs and symptoms of anaphylaxis typically follow a uniphasic course and resolve within hours of treatment. In a minority of cases, these reactions have a biphasic course. The first of such cases were reported in three individuals who, after successfully being treated, experienced symptoms of anaphylaxis after being asymptomatic for 3–4 h (Popa and Lerner 1984). Biphasic reactions have been noted in up to 20 % of cases of anaphylaxis (Tole and Lieberman 2007; Lieberman 2005), but this may be an overestimate. Protracted anaphylaxis is very uncommon and if present is usually seen with profound hypotension; it can last greater than 24 h, is poorly responsive to treatment, and has a poor prognosis (Stark and Sullivan 1986).

Cross-References

▶ Anaphylaxis, Background
▶ Anaphylaxis, Clinical Manifestations and Diagnosis
▶ Etiology of Anaphylaxis
▶ Management of Anaphylaxis
▶ Mast Cell Mediators Associated with Anaphylaxis
▶ Pathophysiology of Anaphylaxis

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Biting Insects (Systemic and Local Reactions)

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Synonyms

Allergy; Anaphylaxis; Arthropod; Bedbug; Beetle; Bug; Caterpillar; Flea; Flies; Hypersensitivity; Insect; Lice; Mite; Mosquito; Spider; Tick

Definition

Biting insects will include non-Hymenoptera arthropods, primarily Arachnida and Hexapoda (true insects), that have been demonstrated to elicit immune-mediated and allergic responses. Hymenoptera and other stinging insects will be addressed in other entries.

Introduction

Cutaneous reactions are commonplace in the management of allergic disease. Hymenoptera, such as wasps and bees, are the focus of much of the literature addressing allergic reactions to insects and rightly so, since there is significant risk of anaphylaxis; however, the focus of this discussion is on biting rather than stinging arthropods. The phylum Arthropoda is the largest of the animal kingdom. The two classes most involved in allergic reactions are Arachnida (spiders, scorpions, mites, and ticks) and Insecta (Hymenoptera, mosquitoes, flies, fleas, bedbugs, lice, beetles, and ants). Biting insects play a significant role with regard to allergic sensitivity, typically in the form of papular urticaria. Insects are very responsive to climate variables such as temperature, rainfall, humidity, and resulting changes in flora and fauna. With the changing climate, there are also changes in ecosystems and therefore opportunities for insects to redistribute. The majority of the geographical redistribution is northward in response to a warming climate.

Systemic reactions, including anaphylaxis, have been reported from many biting arthropods, but the most common reaction is papular urticaria. Papular urticaria is a manifestation of recurrent pruritic papules, vesicles, nodules, and varying degrees of local edema. These reactions are thought to be the result of a hypersensitivity reaction to the salivary proteins of the biting insects. The severity of the eruption and pruritis is related to the host response to these salivary proteins. Children appear to be predisposed to papular urticaria, possibly a reflection of immune mechanisms and/or behaviors that facilitate the encounters.

In papular urticaria, papules are typically grouped in clusters on exposed areas, particularly extensor surfaces of extremities and constricting areas such as the tops of socks and around waistbands, while in some cases, papules may follow a vascular distribution. It has been postulated that papules around constricted areas may represent the effects of local factors such as external pressure, resulting in slowing of blood flow and thereby enhancing precipitation of immune complexes (Heng et al. 1984). Papules may also have a more localized, accessible distribution, such as the torso, neck, and face. The distribution of lesions serves as an important clue in identifying the culprit arthropod. Typically, papules are erythematous, ranging from 3 mm to 10 mm. In the clinical setting, lesions are often excoriated and become secondarily infected, due to the characteristic intense pruritis. Perennial or seasonal exacerbations are common and are presumed to

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be associated with reexposure to the offending arthropod. Recurrence of papular urticaria with reexposure seems to lessen around adolescence and adulthood. This may reflect the development of immune tolerance toward the antigenic proteins (Stibick and Schwartz 2001).

In unexposed subjects, there is no reaction to the first bite. Both the delayed and immediate reactions account for the ensuing papular urticaria. Previously sensitized sites also erupt following the appearance of new lesions, suggesting that circulating antigen triggers the reactivation of sensitized sites which is termed a recall reaction (Alexander 1985). The pathogenesis and exact immune mechanisms of papular urticaria remain somewhat unclear. Heng (Heng et al. 1984) reported granular deposits of C1q, C3, and IgM in the superficial dermal vessels in three subjects with papular urticaria, suggesting that immune complexes with complement activation, through the classical pathway, may be involved in the pathogenesis. A subsequent study by Jordann and Schneider (1997) failed to demonstrate deposition of IgA, IgG, IgM, C3, or fibrin by direct immunofluorescence in 30 patients with papular urticaria. Immunochemistry results did however reveal abundant T lymphocytes and macrophages. Yoshikawa (1985) reported the histology of lesions produced by *Chelacaropsis* sp. mites in six subjects. After 48–72 h of exposure, biopsies of lesions revealed perivascular aggregation of mononuclear cells and slight edema of the papillary dermis.

Although the lesions and pattern of papular urticaria are characteristic, other conditions based on presentation and/or histologic features should be considered.

Arthropoda, "joint-footed animal," is the largest phylum in the animal kingdom. It accounts for approximately 80 % of the animals on Earth, encompassing over 1.5 million described species (Kunkel 1984). The medical impact on man includes transmission of disease as well as morbidity and mortality associated with immune-mediated and toxic reactions after exposure to salivary protein, venom, excrement, or body parts.

Venomous arthropods are found throughout the world. In addition to papular urticaria, arthropods are responsible for more severe, IgE-mediated reactions. These reactions can be limited to a cutaneous event such as urticaria or cause generalized reactions, including life-threatening anaphylaxis. IgE-mediated reactions present with immediate reactivity, often followed by a subsequent, late-phase reaction, up to several hours later. Many deaths due to arthropods go unrecognized, as such, because the signs of envenomation are not noticed.

Contact with arthropods is no longer limited to endemic regions. Venomous arthropods are often transferred inadvertently by shipments of goods. Some examples include the introduction of the red imported fire ant, *Solenopsis invicta*, into the USA from Brazil in 1939 on infested produce (Stafford 1989), and again in the 1950s on an unregulated shipment of azaleas (Schmidt 1977). The imported fire ant now infests more than 160 million acres in 13 states. Further illustrating this point are three cases of scorpion envenomation in Michigan. Other sources include the northern migration in response to a warming climate (Demain et al. 2009).

Arachnida

The class Arachnida includes 65,000 species identified by their four pairs of jointed legs, segmented bodies, large cephalothorax, and hardened (chitinized) exoskeleton. There are several species which attack man. Skin invasion can provide a meal or a site for larval development. Through envenomation or salivation, they may cause pronounced local or systemic symptoms.

Mites

More than 30,000 species of mite and ticks make up the arachnid subclass Acari. Of these, approximately 50 species of mites are capable of causing lesions in human skin. These blood-feeding arthropods are important vectors of pathogens, transmitted in saliva, spreading diseases such as

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scrub typhus, endemic typhus, western equine encephalomyelitis, and rickettsial pox. Cutaneous reaction to mites is usually papular or vesicular with intense pruritis. The saliva of the mite has been identified as the primary source of antigen causing an immediate hypersensitivity (Wikel 1982).

Scabies Mite

Scabies is caused by the infestation by the mite *Sarcoptes scabiei*. A condition common in children and infants, the mites are spread by skin to skin contact and may stay alive in clothing and linen for 2–5 days. The female mite burrows into the skin leaving a trail of eggs and fecal matter (Metry and Herbert 2000). An extremely itchy rash usually follows a 2- to 4-week incubation period. Other family members are frequently infested as well, providing an excellent clue to the diagnosis. Subsequent infestations result in an immediate intense pruritic rash distributed in the interdigital webs, wrists, axillary folds, genitalia, and periareola region (Fitzpatrick et al. 1993). There are several variations of the cutaneous response to scabies infestation. Infants present with a papulosquamous eruption of the head and vesicular eruptions on the feet. Elderly and immunocompromised patients can be infested with Norwegian scabies presenting with diffuse, crusted, excoriated patches covering the entire body including the subungual spaces (Metry and Herbert 2000). Nodular lesions of the groin and axilla may present in 10–15 % of patients with scabies (Burkhart 1983).

The clinical presentation of scabies is thought to represent both local irritation and the development of a hypersensitivity response. Antibody responses during scabies (*S. scabiei*) infestation have been examined. Hancock (1974) demonstrated elevated IgG and IgM and lowered IgA concentrations in the mite infested subjects. Immediate hypersensitivity to *S. scabiei* has been demonstrated by wheal and flare using the Prausnitz-Kustner test, indicating an IgE response to the mite antigen (Maretic 1982). Cross-reactivity between the dust mite, *Dermatophagoides pteronyssinus*, and other arthropods including silverfish, cockroach, and chironomid has also been established, through RAST and RAST inhibition, demonstrating the presence of IgE antibodies against insects in 26 of 82 (32 %) of the dust mite allergic group while only 1 of 67 (1.5 %) in the mite-negative group (Witteman et al. 1995). This cross-reactivity may play an important role in the susceptibility to scabies and its clinical manifestations.

Principal treatment of scabies infestation involves killing the mite and control of pruritis. The scabicides used include permethrin 5 % (Elimite®), 6 % sulfur in petrolatum, or lindane 1 % (Kwell®). Permethrin 5 % (Elimite®) is the scabicide of choice and is applied to the entire body and washed off in 8 h. Most practitioners repeat this treatment in 7 days. In addition to the patient, all family members and close contacts should be treated simultaneously. Bed linen and clothing should be washed in hot water. Persistent pruritis is common due to immunologic reactivity to remaining eggs, feces, or dead mites. The persistent pruritis can be managed with oral antihistamines, cool compresses, and topical or systemic steroids. Secondary infections due to excoriation are treated with appropriate antibiotics.

Chigger Mite

Chigger mites, the larvae of trombiculid mites, have a characteristic bright red coloration and at 0.25–0.5 mm, barely visible to the naked eye. Dermatitis from chigger mites is second in frequency only to scabies mite in causing mite-associated papular urticaria. They ascend to covered areas of skin and are halted by waistbands or belts, resulting in involvement of areas of constricting clothing, usually limited to the waist down. The mite secretes a salivary enzyme onto the skin allowing feeding on semi-digested tissue and extracellular fluid. In non-sensitized patients the lesions are 1–3 mm pruritic papules. Papular urticaria, vesicles or granulomatous reaction, and lymphadenopathy can be seen in

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sensitized individuals. Chigger mites do not burrow into the skin, so warm soapy water may be used to kill and remove the remaining larvae. Symptomatic treatment with oral antihistamines, cool compresses, topical astringents, or topical steroid creams may be beneficial (Smith et al. 1998).

Other Mites

Follicle mites (*Demodex*) are found in sebaceous glands and hair follicles on normal asymptomatic skin and may contribute to the underlying etiology of seborrheic dermatitis and rosacea. Treatment focuses on the resultant disease process (Fitzpatrick et al. 1993).

Grain mites (straw itch mites) are a parasite of insect larvae feeding on grain. The cutaneous manifestations may vary from erythematous maculopapular eruptions to varicelliform lesions. Sensitized patients may also present with fever, malaise, and diarrhea. Treatment for skin manifestations is the same as that for chigger mites (Betz et al. 1982).

There are numerous case reports of papular urticaria resulting from unusual mite infestation, such as exposure to tropical rat mite after extermination of rats (Charlesworth and Clegern 1977). A case of mite dermatitis in a child in California was traced to bats living in the wall (Keh 1974). These situations occur after the preferred host dies out or is eliminated and the animal ectoparasites go in search of an alternate food source.

Ticks

There are many tick species associated with disease in man. In addition to cutaneous reactions, ticks are important vectors of human disease. Hard ticks (*Ixodidae*) are responsible for most tick-related diseases such as *Rickettsia* (Q fever, RMSF, etc.), *Borrelia* (Lymes disease, relapsing fever, etc.), and *Flavivirus* (tick-borne encephalitis). Ticks typically bite during the spring and summer when people spend time in wooded areas. Like many arachnids, ticks have chelicerae, barbed modified mandibles. The chelicerae facilitate firm attachment and a cement-like substance is secreted, allowing the tick to attach and feed up to 7 days (Demain and Taylor 1996).

Most tick bites are painless; in fact, victims are often unaware that they have been bitten. The initial finding is a red papule at the site of the bite, progressing to an extremely pruritic, local swelling followed by the formation of vesicles and ecchymosis. Necrosis and ulceration may occur. Most bites heal within 3 weeks; however, a persistent nodule (tick granuloma) may last for months. Reactions to tick bites likely result from injected toxins, local irritation, or hypersensitivity. Immunologic reactivity, such as a delayed-type IV Gell and Coombs reaction, leads to induration and nodular formation (Jacobs 1988). Immediate type I Gell and Coombs reactions may contribute to the cutaneous reactions. The histology of tick attachment sites has been extensively studied in cattle. Mast cells, eosinophils, and basophils are predominant cell types demonstrated. Additionally, elevated serum histamine after infestation, and a positive Prausnitz-Kustner test, supports immediate hypersensitivity. It is further postulated that this immediate hypersensitivity is an important protective response against blood-feeding arthropods (Metry and Herbert 2000).

Anaphylaxis from tick bites was reported in a paper by Valls et al. (2007). There have been additional reports in the literature of anaphylaxis caused by *Argas reflexus*, a tick found on wild pigeons. *Argas reflexus* are reported to bite man, resulting in allergic reactions ranging from local manifestations to systemic anaphylaxis. Specific IgE has been detected in human sera through IgE immunoblotting (Rolla et al. 2004). Salivary gland antigen of *Argas reflexus* is responsible for the reactions (Metry and Herbert 2000). Commins et al. (2011) reported evidence that tick bites are the cause of IgE-specific antibody to galactose-α-1,3-galactose (alpha-gal), also found in non-primate mammalian meat. Chung et al. (2008) demonstrated that patients with preexisting specific IgE antibody to the antigen

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Biting Insects (Systemic and Local Reactions), Table 1 Preventing tick bites is the most effective method of controlling cutaneous lesions of tick bites and their related serious systemic diseases

1. Proper clothing: long sleeves and long pants tucked into boots
2. Permethrin- or DEET-containing repellents: applied to clothing and skin (Permethrin-treated clothing will maintain effectiveness through several washings)
3. Early detection of ticks to remove them before they embed
4. There have been various proposed techniques for tick removal. The safest and most effective technique is by using forceps to apply gentle, slow reverse traction. Applying oil, petrolatum, nail polish or a lit match to the tick is ineffective and may be harmful
5. Reactivity related to the salivary protein and the remaining mouth parts may result in a tick bite granuloma. A tick bite granuloma may resolve with local injection of corticosteroids, however often requires surgical removal and appropriate antibiotics

in tick saliva, alpha-gal, had a high risk of sensitivity and resultant anaphylaxis to cetuximab, which also contains alpha-gal. In summary, these two studies present compelling data that tick bites are directly related to these specific IgE antibodies.

Preventing tick bites is the most effective method of controlling cutaneous lesions of tick bites and their related serious systemic diseases (Table 1).

Spiders

In the United States, there are an estimated two million spiders in each acre of grassland. All spiders are carnivorous having fangs and venom to catch and immobilize their prey. The venom is produced and stored within poison glands located in the basal segment of the modified jaw, chelicerae. The prey is subdued by the venomous fangs and crushed by chelicerae. The internal structures are predigested with proteases secreted by the salivary gland and sucked through the mouth into the stomach. Despite having eight eyes, most spiders have poor vision and rely on a sharpened sense of touch. It is estimated that in a spider's 1–3-year life span, it consumes over 2,000 insects (Demain and Taylor 1996).

Biting Insects (Systemic and Local Reactions), Fig. 1 Tarantula (Photo courtesy of Jeffrey G Demain)

Of the approximately 100,000 species of spiders, only 50–60 species are reported to bite man. In the United States, four groups of spiders are considered dangerous: tarantulas (*Theraphosidae* spp.), widow spiders (*Latrodectus* spp.), recluse spiders (*Loxosceles spp.*), and the aggressive house spider (*Tegenaria agrestis*) (Steen et al. 2004). There are only a few case reports of possible allergic reactions due spider bites; however, their toxicity can have significant morbidity and mortality (Demain 2003; Jarvinsen 2009).

Tarantula

Tarantulas are among the largest spiders on earth, having a leg span up to 22 cm (Fig. 1). Despite their frightening appearance and fierce reputation, tarantulas are relatively harmless to humans. Tarantulas are wandering nocturnal predators that use their long hairs to feel their prey, compensating for poor eyesight. They have two large fangs to envenomate their victims (Fig. 2). Tarantulas bite only when subduing prey or as a defensive act. Although their fangs can exceed 10 mm in length, the bite of the North American tarantula is described as being similar to an uncomplicated bee sting, and there are no reports of severe reaction or human death. Many species of tarantulas possess urticaria-producing hairs on

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Biting Insects (Systemic and Local Reactions), Fig. 2 Two large envenomating fangs of a tarantula (Photo courtesy of Jeffrey G Demain)

the dorsal surface of the abdomen. When threatened, the tarantula can raise its abdomen and flick the fine hairs at the aggressor, causing pruritic, papular eruption that may last for weeks. This is a common feature of the colorful tarantulas imported from Africa and sold in pet stores (Demain and Taylor 1996; Hunt 1981a).

Black Widow

The widow spider is so named for the belief that the female would devour the male following copulation. In actuality, the female is in a stuporous state after mating, allowing the male to spin a web around her and escape (Wilson 1990). In the United States, there are three varieties of widow spider: the red widow in Florida, the brown widow in the southern states, and the black widow throughout the United States (Wilson 1990).

The black widow (*Latrodectus mactans*) is 6 mm in diameter with a leg span of approximately 4 cm. The red hourglass mark on the underside of the abdomen is characteristic. The widow spider prefers warm, dry climates and is a web weaver. Though the venom in both the male and female is potent, the fangs of the male are too small to penetrate human skin. The reaction following the bite of a black widow is referred to as latrodectism. The venom is an oily yellow fluid made up of six proteins, including a neurotoxin, that produces neuromuscular blockade, in part due to release of acetylcholine and catecholamines, followed by exhaustion of the muscle (Kunkel 1984; Demain and Taylor 1996; Wilson 1990).

There is little initial cutaneous response to envenomation by the black widow; however, a dull aching pain or numbness ensues. Skin manifestations are slight erythema, local perspiration, mild edema, and in some cases lymphangitis. Systemic symptoms begin with local muscle cramps progressing to severe muscle rigidity of the skeletal muscles, particularly the abdominal and leg musculature, lasting up to 48 h. This is followed by nausea, vomiting, salivation, fever, chills, diaphoresis, weakness, tremor, urinary retention, and possibly shock. Cutaneous paresthesias, hyperactive deep tendon reflexes, flexor muscle spasms, and priapism are commonly associated signs. Mortality rates have been reported from 1 % to 5 %, typically among young children, elderly, and immunocompromised (Toewe 1980; Wilson 1990).

Treatment recommendations for systemic manifestations include methocarbamol (Robaxin®) IV, calcium gluconate 10 % IV, and hydrocortisone 100 mg IV every 4 h. Aggressive use of analgesics is helpful in relieving muscle spasms. High-risk patients include children, the elderly, pregnant women, or patients with hypertensive heart disease. For high-risk patients and for those with severe latrodectism, specific antivenom (Lyovac®) is available for IV or IM administration. The neurotoxic effects are usually blocked by the antivenom within 1–2 h. As with any foreign antisera, the package insert should be closely followed for skin testing, proper indications, and precautions (Kunkel 1984; Demain and Taylor 1996; Wilson 1990; Marehec 1983). Cool compresses and elevation can alleviate pruritis and swelling. Other considerations include class I topical steroid ointment and systemic antibiotics when indicated (Fitzpatrick et al. 1993).

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Recluse Spider

The brown recluse spider, *Loxosceles reclusa*, is one of 10 species of Loxosceles. It has short body hair and a characteristic dark brown median band on the dorsum of the cephalothorax in the shape of a violin, hence the "fiddle-back" spider (Fig. 3). Since the recluse is not a web weaver, its habitat may be under rocks, debris, woodpiles, and in undisturbed clothing. As with most spiders, it only bites when provoked, often when the victim reaches into dark areas or when putting on stored clothing.

Biting Insects (Systemic and Local Reactions), Fig. 3 Brown recluse spider (Photo courtesy of Jeffrey G Demain)

The bite of a brown recluse produces a sharp painful bite, often followed by local erythema and vesicle formation. In severe bites, the pain worsens over 8 h and may progress to loxoscelism (necrotic arachnidism). A halo of pallor initially surrounds the bite as a result of arterial spasm, and later there is local hemolysis and bleeding into the area which may continue for several days. The initial reaction is followed by sloughing of the skin, subcutaneous tissue, and possibly muscle leaving a necrotic (volcanic) ulcer (Demain 2003). The wound heals slowly with a great deal of scarring, often requiring surgical repair (Fig. 4). The primary dermonecrotic factor in the venom is sphingomyelinase D, a platelet aggregator, neutrophil chemoattractant, and an activator of thromboxane B2 (Metry and Herbert 2000). Systemic reactions may also occur and include fever, weakness, nausea, vomiting, arthralgia, and petechiae, while others may progress to intravascular hemolysis, progressive jaundice, gross hematuria, and acute renal failure. Death has been rarely reported (Breland 1977). Treatment of a brown recluse bite includes basic wound care, elevation, ice compresses to decrease venom activity, and prophylactic antibiotics. Although systemic corticosteroids are not beneficial for cutaneous wounds, they are considered as first-line therapy for the hemolytic syndrome (King and Rees 1986). Oral dapsone, 100 mg twice daily, inhibits neutrophil function and may be useful for both cutaneous and systemic symptoms (Metry and Herbert 2000; King and Rees 1986; King and Rees 1983). Surgical intervention should be delayed until the wound stabilizes. Antivenom, with activity against sphingomyelinase D, has been developed, but is not yet available for clinical use (Vazquez et al. 2010).

Biting Insects (Systemic and Local Reactions), Fig. 4 Brown recluse spider bite (Photo courtesy of Jeffrey G Demain)

Some other spiders in the USA implicated in human envenomation include wolf spiders (*Lycosa* spp.), jumping spiders (*Phidippus* spp.), and various orb-weaving and the aggressive house spiders (*Tegenaria agrestis*), also suspected of causing necrotic arachnidism (Steen et al. 2004). For uncomplicated bites, treatment is usually local symptomatic care. Awareness that most arthropod bites are not

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inflicted by arachnids reflects the importance of avoiding the assumption that unexplained bites are spiders.

Hexapoda/Insecta (Insects)

The class Hexapoda, "true insects," is characterized by three pairs of legs and three distinct body segments: the head, thorax, and abdomen. In addition, most "true insects" have one or two pairs of wings (Chapman 1998). This class includes the majority of arthropods responsible for adverse reactions, particularly immediate hypersensitivity. Though insects can precipitate direct envenomation effects, significant toxicity is usually associated with multiple stings or bites. Those who work or play outdoors are most commonly affected. Perspiration, increased CO_2 output, warmth, and movement attract certain insects, increasing the likelihood of interaction.

Insects belonging to the order Diptera are ubiquitous and result in billions of human bites worldwide annually. The majority of bites result in minimal skin reactions requiring only symptomatic treatment; serious reactions can occur including life-threatening systemic anaphylaxis. Unlike Hymenoptera, commercial standardized extracts for diagnostic skin testing and allergen immunotherapy are not available. While the majority of significant allergic reactions occur from mosquito bites and several species of biting flies, it is important to remember that any arthropod with a biting apparatus or piercing mouthparts is capable of inflicting a wound and injecting salivary protein so any individual could experience an allergic reaction if they have been sensitized through prior exposure.

Mosquitoes

The main species associated with bite hypersensitivity reactions in humans include *Aedes* sp. (e.g., *A. egyptii* and A. *communis*), *Culex pipiens*, and *Anopheles* sp. *Aedes egyptii* is the carrier of dengue fever and *Culex pipiens* is the carrier of western encephalitis, and both are associated with bite hypersensitivity reactions in humans throughout North America. *Anopheles* spp. are best known for being the vector of malaria, filiariasis, and tropical eosinophilia, but they have been associated with bite hypersensitivity in Finland (Foote and Cook 2005).

There are several facts to consider relevant to human mosquito-bite hypersensitivity. To begin with, only female mosquitoes bite humans. Six seconds of contact after skin puncture is required for subsequent wheal formation in human skin. After the blood meal, the size of the resultant wheal is proportional to the duration of the feeding time (Christophers 1960). Interestingly, mosquito saliva does not contain histamine, but rather there is a high-molecular-weight fraction (>10,000 kd) that is associated with both immediate and delayed cutaneous reactions (Wirtz 1984).

There are four basic types of reactions seen as a consequence of mosquito bites: local reactions (immediate and delayed), severe delayed reactions with scar formation (via a cell-mediated mechanism or Arthus reaction), exaggerated local reactions, and systemic anaphylaxis. Severe reactions to mosquito bites, such as anaphylaxis, are rare although the true incidence, prevalence, and natural history of disabling local reactions and systemic reactions are unknown. A study of 1,059 random blood donors in Canada showed that 18 % had mosquito saliva-specific IgE > 1 S.D. above the mean for mosquito-bite-negative test subjects (Peng et al. 2002 Nov).

Individuals who suffer repeated mosquito bites show an evolution in local skin responses that can be divided into five stages (Table 2) (Feingold et al. 1968). Several research groups from various regions of the world including Canada, Finland, and Asia have published data attempting to characterize the immunologic nature and mechanism of these clinically observed responses. Several studies have demonstrated the presence of specific IgE and IgG to the salivary antigens of various mosquito species, and there appears to be antigen cross-reactivity between various *Aedes* sp. (Peng et al. 1995). A study of 30 subjects with mosquito bites (23 immediate and delayed, six immediate only,

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Biting Insects (Systemic and Local Reactions), Table 2 Mosquito bites: The clinical stages of reactivity

Stage	Reaction observed
I	None: period of induction
II	Delayed skin reactivity
III	Immediate reaction followed by delayed reaction
IV	Immediate reactions only
V	No reactivity

and one delayed only) showed that mean levels of specific IgE and IgG were highest in subjects that had immediate reactions, and there was a direct correlation between the size of the local reactions and the levels of IgE and IgG suggesting the involvement of both type I hypersensitivity reactions and type III immune complex reactions. In vitro lymphocyte proliferation reactions were highest in subjects with delayed reactions, suggesting a type IV, delayed-type hypersensitivity (DTH) reaction (Peng and Simons 1996). Cutaneous basophil hypersensitivity has also been implicated in delayed reactions to mosquito bites (Oka and Ohtaki 1989). Lastly, a study examining 402 children aged 1 month to 18 years showed that mean levels of mosquito saliva-specific IgE and IgG declined with age after early childhood suggesting that natural desensitization may occur (Peng et al. 2004).

Several unique clinical presentations have been described associated with severe delayed cutaneous reactions. Exaggerated local reactions to mosquito bites have been described in AIDS patients treated with AZT (Diven et al. 1988). A DTH reaction resulting in scar formation has been described in a patient with congenital agammaglobulinemia with absent IgE (Shibasaki et al. 1986). Also described is the "Skeeter Syndrome," manifested by large local reactions to mosquito bites associated with fever in young children aged 2–4 mimicking cellulitis (Simons and Peng 1999). Intense delayed bullous skin reactions progressing to hemorrhagic necrosis with cellulitis associated with systemic symptoms of fever, malaise, muscle cramps, lymphadenopathy, hepatosplenomegaly, and renal failure have been described after mosquito bites in humans with natural killer (NK) cell lymphocytosis (Ishihara et al. 2000). In this syndrome, NK cells are highly activated but dysregulated because of chronic Epstein-Barr virus (EBV) infection, and skin biopsy demonstrates NK cell infiltration in the bullous lesions (Adachi et al. 2002). Recent data has shown that $CD4^+$ T cells from such patients markedly respond to mosquito salivary gland extracts suggesting that $CD4^+$ T cells stimulated by mosquito bites may play a key role in the development of mosquito-bite hypersensitivity and NK cell oncogenesis via the induction of EBV reactivation and EBV-oncogene expression, respectively (Asada 2007).

Subjects who experience significant local reactions to mosquito bites should follow common bite/sting management principles which can include use of oral or topical antihistamines for pruritus and topical low-potency corticosteroids to help reduce local swelling. Use of mosquito repellants when outdoors (especially those containing DEET) plus practicing avoidance measures such as limiting outdoor activities around dusk and wearing clothing that minimizes the amount of exposed skin surface can reduce subsequent bite occurrence (Syed and Leal 2008). There is limited published data on use of prophylactic oral antihistamine therapy with one study from Finland of 29 mosquito-bite-sensitive adults undergoing mosquito-bite challenge suggesting that daily treatment with cetirizine and ebastine were superior to loratadine and placebo in reducing wheal size at 15 min post-bite and reducing the degree of pruritus (Karppinen et al. 2002).

For the rare subjects who experience type I-mediated immediate hypersensitivity reactions including systemic anaphylaxis, there is published literature describing successful skin testing and subsequent immunotherapy with mosquito extracts (Srinastava et al. 2007). However, commercial extracts for skin testing and immunotherapy are not readily available limiting the usefulness of this approach.

Biting Flies

Several species of biting flies have been shown to cause skin reactions in humans. The vast majority

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of these reactions are due to toxic and physical properties of insect salivary and contactant proteins, but immunologic mechanisms have been described depending on the host response to insect proteins.

Black flies are members of the Simuliidae family and are a common nuisance to humans engaging in outdoor activities in northern (USA, Canada, UK) and southern latitudes (Africa, Latin America, and New Zealand) during late Spring and Summer, and they spread diseases including river blindness in Africa and Central and South America (Smith 1973). Bites are typically painless but can develop into a painful papule or vesicle that can persist 4–5 days (Owri et al. 1978). Systemic constitutional symptoms can commonly occur (black fly fever) (Wirtz 1984). Typically, symptomatic local treatment is all that is needed. Nonsteroidal anti-inflammatory drugs (NSAIDs) and even systemic corticosteroids can be used for severe systemic constitutional symptoms. There are reports of black fly bites inducing specific IgE antibody formation although severe Type I Hypersensitivity reactions including systemic anaphylaxis are rare (Hoffman 1987). Of note, avoidance measures are difficult for individuals who like to participate in outdoor activities such as gardening, boating, and camping. Also DEET may not be as effective as a black fly repellent.

Horseflies and deerflies belong to the family Tabanidae and bites can be quite painful, making a deep wound with considerable blood flow (Ebeling 1978). There are reports of systemic allergic reactions including anaphylaxis to deerfly (*Chrisoms vitiates*). Specific IgE antibodies to deerfly antigens have been demonstrated by passive transfer skin testing and basophil histamine release assays (Wilbur and Evans 1975). A recent single patient case report describes effectiveness of allergen immunotherapy with deerfly whole body extract in preventing anaphylaxis to subsequent deerfly bites (Hrabak and Dice 2003). More than 30 cases of anaphylaxis due to horsefly bites have also been described, and specific IgE to a 69-kd salivary protein has been identified by immunoblot in a single patient (Hemmer et al. 1998).

Lastly, allergic reactions have been described to the bites of tsetse flies (family Glossinidiae) including an anaphylactic reaction in a lab worker exposed to occupational tsetse fly bites (Stevens et al. 1996).

Fleas

Fleas are small wingless, bloodsucking insects, belonging to the order Siphonaptera. They live as parasites on birds and mammals, which serve as the source of human exposure. Newly emerging fleas become an obligate parasite once on the host; however, they can survive a remarkably long time without a host. In the absence of a host, fleas become very aggressive, provoking severe attacks on individuals moving into an empty home previously occupied by pets. Specialized mouthparts pierce the skin of the host, introducing saliva containing an anticoagulant which facilitates the safe extraction of capillary blood. Bites from fleas are typically below the knee, especially around the ankles. Bird fleas tend to be more aggressive. Certain species, such as the rat flea, transmit bubonic plaque and typhus. Flea saliva is highly antigenic, often resulting in hypersensitivity often presenting as papular urticaria, especially in young children. Like mosquitoes, the human host appears to become desensitized to flea bites over time (Steen et al. 2004; Demain 2003; Jarvinsen 2009). A study on sensitized dogs demonstrated an upregulation of mast cells and release of mast cell tryptase when compared to non-sensitized animals (Von Reudorffer et al. 2003).

Most flea bites resolve without treatment. Secondary infection may occur, requiring topical or systemic antibiotics. Pruritis can be treated with topical corticosteroids and antipruritics, in addition to oral antihistamines (Metry and Herbert 2000; Steen et al. 2004). Effective flea elimination requires removal of all adult fleas as well as immature fleas.

Lice

Lice infestation is becoming increasingly problematic, attributed to increasing resistance to current therapies. Lice invade hairy or

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intertriginous areas, where they take a blood meal every few hours, resulting in extremely pruritic papules. A female louse can lay up to 300 eggs (nits) in her 30-day life span (Steen et al. 2004). Though saliva has been implicated as the allergen, body parts as well as feces have also been included as a potential offending substance. Pech (1943), using intradermal injections of lice feces extract and lice head extract, demonstrated an immediate skin reaction in patients previously sensitized to lice. The immediate wheal and flare reaction was apparent in twenty minutes. The onset of the "delayed-type" reaction appeared within 4–24 h and lasted 24–72 h, producing an area of redness and induration. Studies of bovine skin also reveal hypersensitivity reactions showing infiltration of neutrophils, eosinophils, and lymphocytes in skin lesions (Baron 1987).

Head lice (*P. humanus capitus*) can be transmitted by direct contact or fomites such as brushes, combs, or hats. Usually the only manifestation is pruritis; however, chronic or severe infestation may result in alopecia, cervical adenopathy, and secondary bacterial infection. Head lice are identified by nits and eggs found on hair shafts. The duration of infestation can be estimated by the distance between the scalp and the location of the nits, grayish-white egg capsules, on the shaft of the hairs. Interestingly, this condition is 35 times more likely in Caucasians than African-Americans (Metry and Herbert 2000; Steen et al. 2004; Elgart 1990).

Body lice (*P. humanus corporis*), like head lice, can be transmitted by direct contact or through fomites such as clothing or bed linens. Early infestation is represented by red, pruritic macules typically on the back or axillary creases. Excoriation, lichenification, postinflammatory pigment changes, and persistent urticaria can develop with chronic infestation (Elgart 1990).

Pubic lice (*P. pubis*) produce infestation limited to short hairs. This typically involves the pubic area; however, body hair, axillary hair, beards, eyelashes, and eyebrows can also become infested. This louse is commonly transmitted by sexual contact although fomites may play a role in transmission. Pruritis is usually the only symptom and may take up to 30 days after infestation to develop. Small blue-gray macules (maculae cerulae) on the thighs, buttocks, and suprapubic areas are characteristic. This pigmentation change is thought to be secondary to a reaction of the louse saliva with the host's blood (Steen et al. 2004; Elgart 1990).

Treatment of head and body lice requires killing both the adult lice and eggs with pediculocidal agents. The most frequently used agent is synthetic permethrin 1 % lotion or crème rinse. A single application is left on for 10 min then rinsed off. This therapy is effective in 90 % of cases. A second application is recommended after 7 days. All contacts are treated. Nits (eggs) can be combed out of the hair. All intimate fomites, such as linens, clothing, towels, and hats, must be washed with hot water and dried on high heat (Metry and Herbert 2000; Steen et al. 2004; Elgart 1990).

Treatment of pubic lice requires the same pediculicidal agent described above. Eyelid infestation is treated by (1) physical removal of nits and lice and (2) application of an occlusive ointment, such as petrolatum. Reinfestation after successful therapy is usually due to reexposure to the same sexual partner or linens. Treatment failure may occur secondary to resistance to pediculicidal agents (pymethrin and lindane) or inadequate application to all affected areas (Steen et al. 2004).

Caterpillars

Although not a biting insect, caterpillars are responsible for significant cutaneous and even systemic allergic reactions. Lepidoptera are "scaly, winged insects," encompassing butterflies and moths in all stages of development. There are an estimated 140,000 species in this order, of which 50–150 species can cause lepidopterism, the ill effects of larval and adult butterflies and moths resulting from inhalation, ingestion, direct contact, or envenomation. Lepidoptera have a very complex life cycle. After the male and female mate, the fertilized eggs are deposited onto foliage where they hatch and the larval

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form (caterpillar) emerges. The caterpillar undergoes 5 or 6 developmental molts and transformations known as instars. It is during these early developmental stages that they are a threat to humans. The most mature instar pupates into a cocoon, ultimately emerging as an adult moth or butterfly (Wirtz 1984; Rosen 1990).

Stinging or urticating caterpillars excrete their venom through hollow hairs (setae). Erucism is a term used to describe the envenomation or release of poison by the larval or caterpillar stage. Some caterpillars possess urticating hairs or nettling setae that can release venom when the terminal section is broken or brushed. During the final instar of *Euproctis similis*, there are an estimated 2,000,000 urticating setae per caterpillar (Wirtz 1984; Rosen 1990; Beck 1977). Contact results in immediate burning pain with radiation and a grid-like row of red punctate lesions along the skin path of the caterpillar. Other local lesions include vesicles, hemorrhagic bullae, and eventual lymphangitis with lymphadenopathy (Rosen 1990; Berman and Ross 1983; Hossler 2010a, b).

Though no deaths have been reported, systemic effects can occur within hours, including nausea, vomiting, malaise, fever, headaches, and shock (Wirtz 1984; Hossler 2010a, b). Hypersensitivity including anaphylaxis has also been demonstrated (Vega et al. 2000). Wirtz (1980) reported that 28 % of entomologists surveyed had history of arthropod allergy, of these 67 % were to Lepidoptera. Perlman (1976) demonstrated evidence of both inflammatory and allergic response to this occupational hazard. Clinical and immunological studies including in vitro procedures and direct patient testing confirmed IgE-mediated hypersensitivity, as well as the nonspecific irritation of material from Lepidoptera. Vega et al. (2000) reported allergic reactions associated with exposure to the pine processionary caterpillar (*T. pitocampa*) in Spain. Fifty-five patients with cutaneous, ocular, or respiratory symptoms, in addition to anaphylaxis after exposure in a pine forest inhabited by the pine processionary caterpillar, were studied. Skin prick testing with whole body extract was positive in 32 of 55 symptomatic subjects (58 %) and only 1 of 30 controls. Specific IgE detection by ELISA was inconsistent, thought to be due to the low amount of antigen in the crude extract.

McGovern (1961) reported an epidemic of stings from the puss caterpillar in Texas during the summer of 1958. Based on the responses of 601 physicians surveyed, the natural history and symptoms were described in a reported 2,130 stings. The major symptoms were severe local pain (98 %) and local swelling (92 %). Other symptoms included lymphadenopathy, headache, as well as shock-like symptoms in 5 % and convulsions in 0.2 % of patients. Eight patients were hospitalized, but there were no reported deaths (McGovern 1961). In the summers of 1972 and 1973, there was a significant increase in the Douglas fir tussock moth, resulting in devastation of 890,000 acres of forests in Oregon, Washington, and Idaho (Wirtz 1984). The windborne spread of the caterpillar hairs resulted in symptoms including pruritis, urticaria, along with ocular and respiratory symptoms. Loggers, foresters, and lumber mill workers were most affected.

Four species of caterpillar are frequently encountered in the United States, posing a potentially serious threat for the sensitized victim (1) the Io moth caterpillar (*Automeris* spp.), (2) the saddleback caterpillar (*Sibine stiulea*), (3) the Douglas fir tussock moth caterpillar (*Orgyia pseudotsugata*), and (4) the puss caterpillar or wooly asp (*Megalopyge opercularis*). All reported to cause serious occupational and public health problems (Wirtz 1984; Rosen 1990).

The Io moth caterpillar, most prevalent east of the Rocky Mountains, is 5–8 cm long, pale green, with lateral maroon and white stripes. At the center of each body segment is a partial row of tubercles armed with venomous black and green spines connected to individual poison glands. Contact with this caterpillar produces radiating pain and a pronounced but short-lived wheal surrounded by wide flare (Rosen 1990; Beck 1977).

The saddleback caterpillar, found east of a diagonal line from Massachusetts through the

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Biting Insects (Systemic and Local Reactions), Fig. 5 Megalopyge opercularis (puss caterpillar, wooly slug) (Photo courtesy of Jeffrey G Demain)

middle of Texas, is 2–3 cm long and has a brown sluglike body, covered middorsally by markings that resemble a saddle sitting on a green and white blanket. Along the lateral body, there are four tubercles on which there are stout spines connected at their bases with individual poison glands. Envenomation occurs when the victim brushes vegetation infested with these caterpillars. Once the spines are brushed, the tips break off, allowing the toxin to flow freely onto the skin (Rosen 1990; Beck 1977; Hossler 2010a).

The puss caterpillar, prevalent in southeastern United States, is the larva of the flannel moth. The larvae are seen in a variety of colors ranging from white to dark gray and range in length from 2 cm to 3 cm (Fig. 5). They are completely covered with venomous setae, resembling tufts of cotton, or neatly combed fur in the shape of a Brazil nut (McGovern 1961).

Diagnosis of caterpillar dermatitis is often made by the characteristic, grid-like pattern of erythematous punctures. Microscopic examination of a skin scraping may also reveal the typical barbed setae of the caterpillar. Treatment of cutaneous reactions is limited to symptomatic care. Washing the affected areas with soapy water will help reduce cutaneous pathology. Application of cool compresses, calamine lotion, and oral antihistamines may reduce pruritis. Topical or systemic corticosteroids may also be helpful (Berman and Ross 1983; Delon 1982). Suspected systemic allergic reactions should be treated the same as other causes of anaphylaxis. Precautions should be taken to reduce exposure by wearing gloves, long sleeves, masks, and eye protection when working in endemic areas.

Beetles

There are over 250,000 species of beetles, order Coleoptera, making this the largest order in the animal kingdom (Steffan 1981). Beetles are characterized by a narrow prothorax which connects the head and the base of the wings and range in length from 1 cm to 2 cm. Cantharidin is the substance in their bodies that produce blisters when it contacts with skin. Pressure exerted by clothing or by swatting the beetle on the skin is usually sufficient to cause release of the blistering fluid. Reactions primarily consist of superficial linear bullae. If suspected, promptly washing the affected area with soapy water prevents the formation of vesicles. Cool compresses and topical or systemic steroids may be useful in severe cases. The blister should be left intact to reduce the chance of infection (Demain and Taylor 1996; Steen et al. 2004; Breland 1977).

Reduviid

Reduviid or kissing bugs (*Triatominae protracta*) are widely varying in size and typically nocturnal. Usually they bite their sleeping victims several times during the night in order to take their blood meal, feeding exclusively on the blood of vertebrates (Fig. 6). Reduviids often live near the source of their prey such as bird nests, barns, nests of small mammals, crevices, cracks, or in houses in clothing and linens. Bites and allergic reactions from these hematophagous insects are a significant public health problem (Demain 2003; Hunt 1981).

There are over 4,000 species of Reduviidae, of which approximately 10 are reported to cause severe reactions in humans. They are the vector

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Biting Insects (Systemic and Local Reactions), Fig. 6 Triatoma (kissing bug, conenose bug, assassin bug) (Photo courtesy of Jeffrey G Demain)

for trypanosomiasis, Chaga's disease. Trypanosomes can be found in the digestive track of a small percentage of the Reduviids. Reduviids defecate on the wound after feeding, allowing entry of the trypanosomes into the victim (Edwards 1984). Reduviid bugs are approximately 1 cm to 3 cm long. They are flattened dorsally, enabling them to hide in small cracks and crevices. Often called "conenose bugs," they have a characteristic elongated, cone-shaped nose. Attracted to light and in the absence of their preferred host, they travel toward houses and will readily feed on humans. They take flight in the spring and summer when temperatures are greater than 20° C. Bites are usually on the hands, arms, feet, or face including around the lips, earning another common name, "kissing bug." Their proboscis contains four stylets used to pierce the skin. The bite is generally painless; however, when startled or swatted, they can inflict a painful piercing wound with severe local reactions, including necrosis and ulceration similar to spider bites (Hunt 1981; Edwards 1984; Marshall 1982).

Clinical reactions to reduviid bites vary. Most victims have no reaction and are never aware of being bitten; however, sensitized individuals may have episodes of nocturnal anaphylaxis (Marshall 1982). Studies suggest a 5–7 % prevalence of Triatoma sensitivity, with as many as 30,000 persons in California alone at risk for anaphylaxis (Marshall 1986a; Rohr 1984; Paddock et al. 2001). Four distinct cutaneous reactions have been described: (1) papule with a central punctum, (2) small vesicles grouped around the bite site with edema and erythema, (3) giant urticarial lesion with central punctum and brawny edema, and (4) hemorrhagic nodular-to-bullous lesions (Hunt 1981). Massive extremity swelling and regional lymphadenopathy have also been described. Systemic reactions reported by sensitized individuals include generalized pruritis, urticaria, facial angioedema, laryngeal and glossal edema, gastrointestinal distress, dyspnea, hypotension, syncope, convulsions, and death (Toewe 1980; Wirtz 1984; Hunt 1981; Edwards 1984; Marshall 1982).

Serious cases of systemic anaphylaxis are caused by hypersensitivity to salivary components of these hematophagous insects. A woman with a history of anaphylaxis was desensitized using salivary gland extract developed for this purpose. Success was demonstrated by *Triatoma protracta* bite challenge and radioimmunoassay (Marshall 1982).

Rohr (1984) identified five subjects with Triatoma hypersensitivity, initiated immunotherapy, followed IgE and IgG levels, and interval bite challenges. A successful program of immunotherapy for *Triatoma protracta*-induced anaphylaxis was developed. This program included a new passive extract antigen preparation standardized by RAST inhibition. This antigen facilitated the development of a reliable skin test protocol for in vivo diagnosis of *Triatoma protracta* allergy. Five patients with *Triatoma protracta*-induced anaphylaxis underwent a rapidly increasing dosage schedule of immunotherapy. The IgE and IgG antibody responses during immunotherapy were followed with solid phase RIA. Protection against anaphylaxis was confirmed in all patients with a bite challenge by *Triatoma protracta*.

Marshall (1986a) looked at cross-reactivity among different species of Triatominae. He demonstrated, by RAST inhibition, that binding of IgE antibodies to *T. protracta* antigen was not inhibited by salivary extracts from *T. rubida*, *T. cavernicola*, *T. rubrofasciata*, or *Rhodnius prolixus*, emphasizing the importance of species identification and species-specific antigens for diagnosis and immunotherapy. The major salivary protein of *T. protracta*, procalin, has been

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identified (Paddock et al. 2001). Procalin is responsible for 89 % of its allergenic activity of *T. protracta*. Procalin has recently been cloned, potentially providing quantities of antigen for ongoing investigation, serologic testing, and possibly commercially available immunotherapy (Paddock et al. 2001; Marshall 1986a).

Reduviid immunotherapy is not yet commercially available. Anaphylactic reactions should be treated the same regardless of the etiology. Environmental controls to reduce the risk of further bites are also critical. Treatment for local skin reactions is symptomatic with cool compresses and class I topical steroids. Oral antihistamines may also be beneficial.

Bedbugs

The common bedbugs (*Cimex lectularis and Cimex hemipterus*) have made a resurgence in recent decades. The increase is thought to be associated with more international travel and resistance to pesticides. After taking a blood meal, they leave the human body; however, they can successfully travel in luggage and on clothing infesting other locations (Crissey 1981).

The bedbug is a nocturnal feeder. Bites are often multiple and clustered in an irregularly linear distribution. Reactions to bites are typically papules and wheals with a central hemorrhagic punctum; however, bullous lesions are not uncommon (Steen et al. 2004). The bites can be severely pruritic and can become secondarily infected due to scratching. Sensitized individuals can develop papular urticaria which has been shown to represent a late-phase, IgE-mediated reaction to the salivary protein, nitrophorin (Lverkus et al. 2006).

In addition to the characteristic bites, other indicators of bedbugs include small blood dots on linens and a violet stain seen along the mattress seam, representing bedbug fecal staining. Eradication of bedbugs is difficult and most effectively done by heating the affected room to over 112° F by professional exterminators. Barrier covers for the mattress and pillows may also be effective.

Management of Local Reactions to Biting Insects

Symptomatic treatment of papular urticaria and other cutaneous reactions to arthropod bites remains the cornerstone of management. Washing involved skin promptly with soapy water often removes both the ectoparasite and the offending toxic or allergenic substance. Cool compresses provide symptomatic relief of discomfort and pruritis. Antihistamines remain a mainstay in reducing the severe pruritis often accompanying papular urticaria. Quick acting antihistamines such as hydroxyzine and diphenhydramine are most effective, although sedation is a major concern. Second-generation antihistamines such as cetirzine have been shown to be beneficial in both symptomatic and possibly prophylactic symptom control while reducing the risk of sedation. Prophylactic treatment with cetirizine and ebastine in mosquito-sensitive individuals significantly reduces the immediate wheal and accompanying delayed response of papular urticaria (Karppinen et al. 2002). The use of topical corticosteroids, especially potent (class 1) steroids, is widely used in treating papular urticaria although benefits are inconsistent and reports are anecdotal (Howard and Frieden 1996). Topical doxepin may also reduce itching; however, it is not approved for use in children and may also cause sedation. Other topical preparations such as camphor, menthol, or praxomine may benefit some patients (Howard and Frieden 1996). Severe pruritis prompts scratching and excoriation of the papules setting up a risk of secondary infection. Early treatment with topical antibiotics such as mupirocin is often warranted, although appropriate systemic antibiotics are often indicated, especially in high-risk situations. Recommendations for prevention and treatment of specific arthropods have already been discussed.

Conclusion

Hypersensitivity reactions to biting and stinging arthropods remain a significant economic,

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epidemiologic, research, and medical challenge. Most species produce a localized area of cutaneous response, but serious systemic reactions and even fatalities continue to occur. Standard techniques are used to test emergent and acute reactions, and specific immunotherapy can be attempted in well-defined instances. There is a wealth of opportunity for research to further clarify this important and neglected area of immune response and morbidity.

Cross-References

- Biting Insects (Systemic and Local Reactions)
- Delayed Anaphylaxis to Mammalian Meat (Alpha-Gal)
- Diagnostic Components: Allergen for In Vivo (Skin Testing, Immunotherapy) and In Vitro (Serology) IgE Antibody Testing
- Diagnostic Terms: Atopy
- Honeybee Allergy
- IgE Testing
- Immunotherapy, Mechanisms
- Imported Fire Ant Allergy
- Insect Allergy in Children
- Role of IgE in Disease
- Role of Mast Cells in Diseases
- Specific IgE
- Venom Content
- Vespid Allergy: Yellow Jackets, Hornets and Wasps

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Bronchial Challenges

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Synonyms

Bronchoprovocation testing

Definition

Bronchial challenges are tests that use one of several triggers to identify airway hyperresponsiveness, or the state of heightened bronchoconstrictive response to airway stimuli.

Essay

Bronchial challenges, or bronchoprovocation tests, are used to identify airway hyperresponsiveness (AHR) in order to help support or call into question a diagnosis of asthma. AHR, also known as bronchial hyperresponsiveness, is a state of heightened bronchoconstrictive response to airway stimuli (Katial and Covar 2012). Although AHR is a hallmark of asthma, asthma is not the only condition that leads to AHR. A limited differential diagnosis of AHR is shown in Table 1.

Direct and Indirect Challenges

There are several different methods of challenging the airway in order to assess for AHR. Bronchial challenges can be categorized as either direct or indirect challenges, several of which are shown in Table 2.

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Bronchial Challenges, Table 1 Differential diagnosis of AHR

Differential diagnosis of AHR
Asthma
Chronic Obstructive Pulmonary Disease (COPD)
Congestive Heart Failure (CHF)
Cystic Fibrosis (CF)
Bronchitis
Allergic Rhinitis

Data taken from (Katial and Covar 2012)

Bronchial Challenges, Table 2 Direct versus indirect bronchoprovocation testing in asthma

DIRECT	INDIRECT
Methacholine[a]	Exercise[a]
Histamine	Mannitol[a]
Prostaglandins	Cold Air[a]
Leukotrienes	Allergen[a]
	Irritant[a]
	Hypertonic Saline[a]
	Eucapnic Voluntary Hyperpnea (EVH)[a]
	Propanolol
	Bradykinin
	Adenosine 5'-Monophosphate (AMP)

Data taken from (Cockcroft and Davis 2009) and (Cockcroft 2008)
[a]Approved for use in North America

Direct challenges generally act on the airway smooth muscle, mucus glands, and/or microvasculature directly to cause bronchoconstriction. Methacholine and acetylcholine, for example, act on muscarinic receptors. Histamine, on the other hand, acts directly on the histamine receptors. Both muscarinic and histamine receptors are located on the airway smooth muscle. Histamine, which tends to cause more adverse effects such as cough, flushing, and even syncopal reactions than does methacholine, is no longer approved for use in North America (Cockcroft and Davis 2009). Nonetheless, previous comparisons of methacholine and histamine challenges suggest that the two yield almost identical results (Juniper et al. 1994).

Unlike direct challenges, indirect challenges do not act directly on structures of the bronchial tree to cause bronchoconstriction, but rather do so through their effect on inflammatory and neuronal cells. Once stimulated, these cells release mediators and cytokines which, in turn, act on airway smooth muscle to cause bronchoconstriction (Cockcroft and Davis 2009). In general, indirect challenges tend to be less sensitive but more specific than direct challenges for the diagnosis of asthma (Parkerson and Ledford 2011; Sverrild et al. 2010).

For a more detailed description of methacholine challenge, mannitol challenge, and exercise challenge, please see the separate encyclopedia entries entitled: *Methacholine Challenge, Mannitol Challenge*, and *Exercise Challenge*. The *Methacholine Challenge* entry also discusses medications that might interfere with test results and how long these medications should be held prior to testing. A brief comparison of methacholine and mannitol challenges is included in the *Mannitol Challenge* entry. Bronchial challenges that look for bronchial hyperresponsiveness to a specific trigger are discussed below.

Challenges Using Specific Triggers

Other challenges that are important, though less frequently performed, are those assessing the bronchoconstrictive effect of specific triggers, such as irritants, allergens, or occupational exposures. Common irritant triggers include perfume or cigarette smoke, but any irritant can be assessed in a similar manner. A laryngoscopy performed immediately after an irritant challenge can help distinguish between irritant-induced asthma, irritant-induced vocal cord dysfunction, or a combination of the two.

Specific challenges are often used in the diagnosis and management of occupational asthma, where assessments in and out of the workplace yield important information regarding the effect of specific occupational exposures on lung function. Allergen challenges, on the other hand, are most often used in the clinical research setting. Because the asthmatic response to an allergen can consist of both an immediate and delayed phase, patients undergoing these challenges must be monitored for a longer period of time. Challenges

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Bronchial Challenges, Table 3 Absolute and relative contraindications for bronchial challenges

Absolute contraindications for bronchial challenge
FEV1 <50 % predicted or <1.0 L
Severe hypertension (systolic BP > 200 mmHg or diastolic BP > 100 mmHg)
Acute coronary syndrome within 3 months
Cerebrovascular attack within 3 months
Cerebral or aortic aneurysm
Relative contraindications for bronchial challenge
FEV1 <60 % predicted or <1.5 L
Pregnancy or lactation
Hypoxemia (PaO2 < 60)
Respiratory infection in the past 6 weeks
Inconsistent or unacceptable baseline spirometry
Failure to withhold medications that can interfere with testing
Use of cholinesterase inhibitor medication (most common use is myasthenia gravis)

Data taken from (Crapo et al. 2000) and (Cockcroft 2008)

using specific triggers can be helpful in validating or disproving a patient's concern regarding the ability of a given environmental trigger to cause bronchoconstriction. Unfortunately, they are difficult to perform since they require access to an exposure chamber, which is not often readily available, or workplace assessments, which can be tedious or even impossible depending on the type of occupation at hand. In addition, there is no standardized dose for most of these specific challenges, so they can yield false-negative results if too little of the exposure in question is used during the challenge.

Contraindications to Bronchial Challenges

As shown in Table 3, there are several absolute and relative contraindications for bronchial challenges.

Most of these contraindications were developed with safety in mind since performing a bronchial challenge on a pregnant patient or on one with unstable respiratory, cardiac, or cerebrovascular disease would carry an unacceptable risk of hurting the fetus or exacerbating these underlying conditions, with potentially serious or even fatal consequences. The remaining relative contraindications are in place to ensure accuracy of testing since they would be likely to yield false-negative or false-positive results.

Cross-References

- ▶ Exercise Challenge
- ▶ Mannitol Challenge
- ▶ Methacholine Challenge

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Bronchiectasis

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Synonyms

Large airway disease

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Definition

Bronchiectasis is a disease state characterized by localized and/or diffuse, permanent dilation of the large airways caused by destruction of the muscle and elastic tissue.

Introduction

On imaging or histopathology, the bronchial dilation in bronchiectasis may present in a variety of ways including cylindrical, varicose, or cystic (or saccular) distension depending on the specific underlying cause and may be seen in association with bronchiolectasis (dilatation of the bronchioles) (Reid 1950). The cystic type is the most severe variant. Bronchiectasis may be idiopathic, congenital, or acquired as the result of infectious or noninfectious manifestations of systemic (e.g., rheumatoid arthritis) or lung-limited diseases (e.g., postpneumonia).

Epidemiology/Prevalence

In the advent of antibiotics and vaccinations, the prevalence of bronchiectasis specifically infectious causes has probably decreased since the mid-twentieth century (Barker 1995). Multiple factors influence the prevalence of bronchiectasis such as the type of population studied (e.g., geographic location, socioeconomic conditions, and access to health care), study methodologies and data source, and diagnostic imaging utilized (e.g., chest films vs. high-resolution computed tomography scanning). On a review of US insurance claim database from outpatient and inpatient settings, the prevalence of bronchiectasis was estimated to be 52.3 cases per 100,000 adults (Weycker et al. 2005). In another study in the USA, the average annual age-adjusted hospitalization rate from 1993 to 2006 was 16.5 hospitalizations per 100,000 population (Seitz et al. 2010). From 1993 to 2006, the age-adjusted rate increased significantly, with an average annual percentage increase of 2.4 % among men and 3.0% among women. The highest rate of bronchiectasis-associated hospitalizations was observed in the oldest age groups and in older women in particular (Seitz et al. 2010).

Pathogenesis and Causes

Bronchial dilation secondary to deficiency or loss of elastin and/or destruction of muscle and cartilage may be secondary to intrinsic or extrinsic airway (e.g., neighboring lung tissue) mechanisms in isolation or in combination (Mallory 1947; Reid 1950; Currie et al. 1987; Loukides et al. 2002; Chan et al. 2009; Pasteur et al. 2010). Although investigation of the causative factors in patients with bronchiectasis may be unrevealing, the recognition of the specific cause may have prognostic and treatment implications (Pasteur et al. 2010). Common causes include (I) mucociliary disorders (e.g., Kartagener's syndrome, Young's syndrome), (II) immunodeficiency states (e.g., combine immunodeficiency disorders), (III) systemic autoimmune disorders (rheumatoid arthritis, inflammatory bowel disease), (IV) superimpose infection in susceptible individuals (allergic bronchopulmonary mycosis), (V) postinfection (e.g., pneumonia), (VI) traumatic (e.g., lung injury), (VII) obstructive (e.g., chronic acid reflux or foreign body aspiration, endobronchial tumor), (VIII) partial genetic defects (e.g., cystic fibrosis transmembrane regulator mutations), (IX) congenital (e.g., primary ciliary dyskinesia), (X) anatomic defects (e.g., middle lobe, Williams-Campbell syndrome, and Mounier-Kuhn syndrome), and (XI) idiopathic fibrotic interstitial pneumonias (e.g., traction bronchiectasis).

Clinical Manifestations

In general, patients with bronchiectasis complain of daily cough and mucopurulent sputum production. The volume of sputum produced in 24 h has been used to grade the severity of clinical symptoms such as breathlessness: mild (<10 ml), moderate (10–150 ml), and severe

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(>150 ml) (Ellis et al. 1981). Patients may also present with dyspnea on exertion, bronchospasm, intermittent episodes of acute respiratory exacerbations or bronchitis, and constitutional symptoms such as fatigue, weight loss, and hemoptysis. Hemoptysis when observed is commonly mild; however, bronchiectasis is one of the most important causes of massive hemoptysis resulting from erosion or rupture of tortuous and hypertrophied bronchial arteries (Swanson et al. 2002).

Diagnosis

High-resolution computed tomographic scanning is the most sensitive and commonly initial diagnostic modality of choice (Munro et al. 1990). The type, distribution, and pattern of bronchiectasis on imaging may provide etiologic clues (Cantin et al. 2009) before the clinician embarks on a diagnostic evaluation that includes taking an in-depth medical history with focus on the severity and course of respiratory symptoms, comprehensive occupational and environmental histories, a full systems review, and a thorough physical examination necessary for an accurate diagnosis of the potential cause.

Pulmonary function testing is useful for quantifying the extent of pulmonary impairment. An obstructive pattern is commonly observed in patients with bronchiectasis. A bronchodilator response has been documented in up to 46 % of patients (Hassan et al. 1999).

Sputum microbiologic cultures in stable non-cystic fibrosis bronchiectasis frequently include Haemophilus *influenzae* and Pseudomonas *aeruginosa* (Angrill et al. 2002; King et al. 2007). Isolation of Aspergillus *fumigatus* on cultures may raise the possibility of allergic bronchopulmonary aspergillosis in patients with poorly controlled asthma or cystic fibrosis, while nontuberculous mycobacterial infection (e.g., Mycobacterium avium-intracellulare) may be seen in subjects with impaired host defenses or with chronic structural lung disease.

In patients with bronchiectasis, other specific testing (e.g., quantitative immunoglobulins, testing for cystic fibrosis transmembrane conductance regulator gene mutations, esophageal manometry and pH testing, tuberculin skin test, bronchoscopy) should be pursued based on clinical suspicion.

Integration of the clinical, physiological, radiographical, and laboratory data is required for the correct diagnosis of the conditions associated with bronchiectasis (Pasteur et al. 2010).

Management

Treatment of bronchiectasis is aimed at treatment of the underlying condition (e.g., immunoglobulin or alpha-1-antitrypsin replacement therapy), prevention (e.g., pneumococcal and influenza vaccinations), supportive measures, and surgical removal of destroyed lung when medical therapy is unsuccessful or to control massive hemoptysis and recurrent infectious respiratory exacerbations arising from lung areas (e.g., lingual or right middle lobe) sometimes harboring resistant organisms (Pasteur et al. 2010).

Supportive measures include (I) supplemental oxygen when needed, (II) treatment and prevention of comorbid conditions such as gastroesophageal reflux and bronchial hygiene (e.g., airway clearance techniques, mucolytic agents), (III) medical therapy (e.g., bronchodilators, inhaled corticosteroids) and suppression of antimicrobial load (i.e., antibiotics), (IV) smoking cessation, and (V) maintenance of nutrition and pulmonary rehabilitation therapy.

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C

Cobalt Contact Dermatitis

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Synonyms

Cobalt (II) chloride-hexahydrate; Cobalt blue; Cobalt chloride; Cobalt dichloride, hexahydrate; Cobaltous chloride; Cobaltous chloride, hexahydrate; Hexahydrate

Definition

Cobalt contact dermatitis is a cutaneous adverse reaction which occurs after exposure to cobalt.

Introduction

People are widely exposed to metal allergens in their daily routine. Cobalt is a metal found naturally in soil, dust, and seawater. It is a silvery metal with many properties similar to those of iron and nickel and it is used with other metals to make metal alloys. It adds strength to alloys when used in combination with other metals, such as nickel, chromium, tungsten, and molybdenum. It is usually found in association with nickel. It is a common metal and the most frequent means of prolonged skin contact to it is in jewelry. It may also be widely released from leather items, as it is used in the so-called premetallized dyeing of leather products (Thyssen et al. 2013). Symptoms usually occur when the article comes into contact with the skin.

Epidemiology

Sensitization to nickel, cobalt, and chromium is frequent in patch test populations. The prevalence is affected by geographical and sociocultural factors. Cobalt sensitization uncommonly occurs as an isolated sensitization, but it is often accompanied by chromium sensitization in men and nickel sensitization in women.

It has been observed that the temporal trend of cobalt allergy tended to deviate from that of nickel. It has been suggested that increased use of cobalt in consumer products and jewelry (as a possible nickel substitute) could cause such a trend (Rui et al. 2012).

Risk factors for allergic contact dermatitis (ACD) include the inherent sensitizing potential of the allergen, its concentration, high frequency and long exposure, occlusion, the presence of factors which increase the penetration of the allergen, and functional skin barrier changes. Contact dermatitis occurs less frequently in the first months of life and its prevalence increases over the years (Brandao and Gontijo 2012).

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Cobalt Exposures and Causes of Dermatitis

Exposure to cobalt can occur in an occupational setting. Occupational cobalt exposure and sensitization have traditionally been observed in metal workers, pottery workers, and bricklayers (Yoshihsa and Shimizu 2012; Thyssen 2012). Cobalt may also be present in other occupations, such as those involving unsaturated polyester resins. These resins are widely used in the manufacture of reinforced plastic products for the marine, transportation, and construction industries (Cahill and Andersen 2010).

There are strong indications that cobalt can be found in leather and textiles. Studies are required to clarify whether cobalt is present in all leather product categories and whether certain colors of leather should be particularly suspected (Thyssen et al. 2013). Detergents and cosmetics may also contain cobalt (Brandao and Gontijo 2012).

Numerous sources of cobalt exposure exist, as shown below (Rietschel and Fowler 2008; Khatami 2013):

1. Home/personal sources:
   - Cobalt blue pigment in porcelain, glass, pottery, ceramics, and enamels.
   - Cobalt in blue and green watercolor paints, and crayons.
   - Metal-plated objects (buckles, buttons, zippers, snaps, costume jewelry, utensils, tools).
   - Medical uses (metal prostheses, dental plates, vitamin B12 preparations for the treatment of anemia).
   - Hair dyes; cobalt pigment produces light brown shades of hair.
   - Antiperspirant preparations.
2. Work sources:
   - Used as binding agent in hard metals to create drills, cutting tools, mechanical parts.
   - Cobalt naphthenate is a common catalyst in the manufacture of polyester resins.
   - Manufacture of cobalt-containing alloys.
   - As an oxidizing agent in automobile exhaust controls, in the rubber tire industry, and in electroplating.
   - Cement industry; cement contains cobalt oxides.
   - Cobalt siccatives or dries are found in certain paints and varnishes.
   - Binding agent in the carbide industry.
   - Wet clay containing cobalt used by pottery workers.

Clinical Picture

Cobalt is a strong skin sensitizer and penetrates the skin and causes contact sensitization and ACD (Wahlberg and Boman 1978). Typical symptoms include redness, swelling, itching, and fluid-filled blisters. Reactions to contact with cobalt also include irritant dermatitis. Cobalt allergy may also trigger an erythema multiforme-like eruption.

It may also cause an airborne contact dermatitis (Rietschel and Fowler 2008; Thyssen 2012). Cobalt exposure via inhalation may also lead to cobalt-related asthma. Hard metal workers may develop cough, wheezing, and dyspnea (Yoshihisa and Shimizu 2012).

Contact dermatitis to cobalt is usually produced by external exposure of the skin to an allergen; however, sometimes a systemically administered allergen may reach the skin through the circulatory system and thereby produce systemic contact dermatitis (SCD). SCD is an inflammatory skin disease which is known to occur with exposure to drugs, foods, and dental metals (Yoshihisa and Shimizu 2012). SCD may be caused by oral intake of cobalt-containing food. Cobalt is part of vitamin B12. Foods with high cobalt content include liver, fish, nuts, and cereals (Thyssen 2012).

Cobalt can even elicit both cutaneous and extracutaneous allergic reactions from chronic internal exposure. Patients may also develop delayed-type hypersensitivity reactions to metals following the insertion of intravascular stents, dental implants, cardiac pacemakers, or implanted gynecologic devices (Basko-Plluska et al. 2011). Implantable cardiac devices play an important role in decreasing the morbidity and mortality in patients with cardiovascular disease.

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Tissue-device interactions leading to systemic hypersensitivity are rarely reported or are perhaps misdiagnosed as infectious in origin (Andrews and Scheinman 2011).

In many cases, allergic reactions are not caused solely by cobalt sensitization. Nickel and cobalt are always found together in alloys and salts, because it is too costly and impracticable to separate those two metals (Rietschel and Fowler 2008). Cobalt is often found in combination with chromium, which may explain frequent instances of co-sensitization to cobalt and chromium (Khatami et al. 2013). However, today the market price of cobalt has led to the extraction of cobalt from mined nickel, resulting in expectedly overall diminished consumer cobalt exposure (Thyssen 2012).

Diagnosis

The diagnosis is based on clinical history, with emphasis on previous exposure. A delay in the onset of the reaction of 24–48 h after exposure to the allergen may make it difficult to establish a causal relationship. A detailed history of events during the week preceding the onset of symptoms should be obtained. The most useful and reliable method for the diagnosis of ACD is the patch test (Brandao and Gontijo 2012).

Epicutaneous patch testing has been used to diagnose metal sensitivity. It is the primary tool to diagnose allergens which cause allergic contact dermatitis. The main advantages of patch tests are that they can be completed without hospital surveillance since they rarely induce adverse reactions. Therefore, a patch test evaluation is the gold standard for detecting metal hypersensitivity.

Cobalt chloride is one of the most frequent allergens to elicit reactions on patch testing. Patch testing is typically done with 1 % cobalt chloride in petrolatum (Thyssen 2012).

Oral metal challenges with metals such as cobalt are sometimes performed and are diagnostic for metal allergies, especially SCD (Yoshihisa and Shimizu 2012).

Management of Cobalt Allergy

It is often difficult to determine the clinical relevance of positive patch test reactions to cobalt chloride, and especially in consumer cases, as the source of cobalt is often not evident (Thyssen et al. 2013).

The only long-term management strategy for cobalt allergy is to identify possible sources of contact and avoid coming into direct contact. It is advisable to avoid contact with cobalt, especially in moist or sweaty conditions, such as keys held in hand or change in pockets. When avoidance is not achievable, there are several methods which can be used to reduce exposure (Rietschel and Fowler 2008):

- Use of metal instruments which have plastic or wooden handle grips.
- Wear vinyl or rubber gloves to avoid direct contact.
- Avoid metallic costume jewelry. Sterling silver and platinum jewelry is usually well tolerated.
- Items such as keys can be coated with several layers of nail polish (which can form a barrier between the skin and the jewelry or other items).
- In the workplace, wear protective clothing and employ no-touch techniques. Identify potential sources of exposure using Material Safety Data Sheets (required for all chemicals and substances which you may come into contact with in the workplace).

It has also been proposed that a low-cobalt diet reduces the dyshidrotic eczema flares in cobalt allergic patients (Stuckert and Nedorost 2008). Therefore, the ingestion of increased amounts of cobalt through food should be added to the list of triggering factors for SCD (Yoshihisa and Shimizu 2012).

Once the dermatitis appears on the skin, treatment is the same as for any acute dermatitis or eczema. Symptoms may be alleviated with topical steroids, antibiotics (for secondary infections), and moisturizing creams.

Antihistamines or immunosuppressive therapy can be used to treat the symptoms. Oral and topical corticosteroids have a supporting role and

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should be used for short periods. It should be considered that the use of topical corticosteroids leads to the risk of atrophy, telangiectasias, tachyphylaxis, and systemic absorption, especially in areas of high sensitivity such as face and flexures. Topical immunomodulators such as pimecrolimus and tacrolimus provide a steroid-sparing option (Brandao and Gontijo 2012).

New consumer items should continuously be considered and investigated for metal release when patients with positive patch test results to metal allergens are evaluated (Hamann et al. 2013).

What Products May Not Contain Cobalt? Truetest.com [Internet]

- Stainless steel, plastic, gold (18 k) or silver jewelry, or decorative items
- Stainless steel tools and utensils or any with plastic coated handles
- Titanium or stainless steel orthodontic materials and ceramic brackets
- Organic nonmetallic pigments for paints, enamels, inks, and glazes

Cross-References

- ▶ Allergen Avoidance: Avoidance Strategies for Skin Allergies
- ▶ Allergic Contact Dermatitis
- ▶ Contact Allergy to Hair Dyes
- ▶ Contact Dermatitis Due to New Metals
- ▶ Nickel Allergic Contact Dermatitis
- ▶ Nickel Contact Dermatitis
- ▶ Topical Corticosteroids

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Contact Allergy to Black Henna Tattoos

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Synonyms

Black henna pseudo-tattoos; Black henna temporary tattoos

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Definition

Contact allergy to black henna tattoos is an acquired delayed-type hypersensitivity (type IV according to Gell and Coombs) to black henna from its application to the skin in the form of a temporary tattoo, leading to allergic contact dermatitis. Black henna is the combination of (red) henna, which is the dried and powdered leaf of the evergreen shrub *Lawsonia inermis*, and the dye *p*-phenylenediamine.

Introduction

Henna is the dried and powdered leaf of the dwarf evergreen shrub *Lawsonia inermis*. Henna preparations, which are usually made by adding water or oil to henna powder or to ground fresh henna leaves, have been used as a dye for the skin, hair, and nails for over 4,000 years and as an expression of body art ("body painting"), especially in Islamic and Hindu cultures in the Arab, African, and Indian world. The pigment lawsone in henna interacts with the keratin in the skin, hair, and nails to give them a reddish-brown color (hence the synonym red henna). Such "temporary tattoos" last approximately 2–6 weeks, until the outer layer of the skin exfoliates. The use of red henna is generally safe and rarely results in allergic reactions or other side effects (De Groot 2013).

In the past 15 years, a new mode of henna application, the so-called temporary black henna tattoo (also sometimes called skin painting, pseudo-tattooing), has become fashionable, ever since the Spice Girls decorated themselves with these body designs. These temporary tattoos are usually applied to young people and children in holiday resort areas on all continents or at festivals and fairs by street tattoo artists with mobile studios but are also available as do-it-yourself kits and ready-to-use henna paste. In contrast to permanent tattooing, it is a painless procedure that involves no needles, as the dye is applied by brushes or special pens on the skin. Black henna is the combination of red henna and *p*-phenylenediamine (PPD) and/or structurally related dyes.

p-Phenylenediamine (PPD) is added to henna to accelerate the dyeing and drying process to only 30 min, to strengthen and darken the color, enhance the design pattern of the tattoo, and make it last longer. These tattoos stain the skin black and have the appearance of a real tattoo.

Since 1997, black henna tattoos have been increasingly reported as a cause of contact allergy and – often fierce – allergic skin reactions in children, adolescents, or young adults. The sensitization is caused by the dye *p*-phenylenediamine (PPD). These patients may later manifest allergic reactions when coloring their hair with (semi)permanent hair dyes or having skin contact with products containing PPD or structurally related chemicals, such as clothes, rubber (Hald et al. 2013), or medicaments. The sensitization of children to PPD may have important consequences for health and later career prospects. Review articles on this topic include Marcoux et al. (2002) (up to 2001), Calogiuri et al. (2010), and De Groot (2013) (a comprehensive fully referenced review of side effects of red and black henna including contact allergy to black henna tattoos from the author of this chapter).

Epidemiology

Several questionnaire studies have shown that the number of people who have had one or more black henna tattoos is considerable: 6 % of the general Danish population aged 18–70 and 7 % of adults and 14 % of their children in the UK. Higher percentages (14–33 %) were observed in selected younger age groups with a 40–50 % exposure in young Danish (mostly female) hairdressers and hairdressing apprentices (Orton 2008; Hansen et al. 2010; Bregnhøj et al. 2011). It has been estimated that of all people who have their skin tattooed with black henna, some 2.5 % will become allergic to it (De Groot 2013).

In the English medical literature, over 140 patients sensitized by tattoos have been reported (De Groot 2013). Among these were several case series of 5–31 patients (Jappe et al. 2001; Chung et al. 2002). Some clinics diagnosed ten

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patients with tattoo reactions within a 6–7-month period (Chung et al. 2002). Not infrequently, siblings have developed allergic reactions from a tattoo that had been applied at the same time (Jappe et al. 2001; Spornraft-Ragaller et al. 2012). Many cases and case series of (often fierce) reactions to other PPD-containing products, notably hair dyes, have been reported in patients previously sensitized by a tattoo (Søsted et al. 2006; de Groot 2013). In some clinics, from 5 to up to 21 % of all cases of contact allergy to PPD as shown by positive patch test reactions to the dye were attributed to previous black henna tattoos (Patel et al. 2007).

All data taken together, and considering that only a minute fraction of patients with allergic reactions to black henna tattoos are published in literature, it is safe to assume that contact allergy to and allergic contact dermatitis from black henna tattoos occur frequently. Most patients are children, adolescents, or young adults with a female preponderance. In older age groups, the use of henna tattoos, and consequently allergic reactions to them, is limited (Hansen et al. 2010).

Etiology and Pathogenesis

Allergic reactions to black henna tattoos are the result of the development of contact allergy (delayed-type hypersensitivity, type IV hypersensitivity according to Gell and Coombs) to PPD. Most patients with tattoo allergic contact dermatitis have become sensitized to this dye from (its presence in) the tattoo itself. Others were already contact allergic to PPD, mostly from previous tattoo exposure, less often from hair dyeing of other exposures to PPD or structurally related chemicals. The factors contributing most to the sensitization reactions are the extreme sensitizing capacity of PPD and the high concentrations of the dye in henna preparations, often more than 6–10 % (Akyüz and Ata 2008) and sometimes more than 25 %. Other factors favoring the development of contact hypersensitivity, e.g., by enhancing penetration of chemicals from the tattoo material into the skin, are shown in Table 1.

Contact Allergy to Black Henna Tattoos, Table 1 Factors favoring the development of contact allergy to *p*-phenylenediamine in black henna tattoo (Jappe et al. 2001; Akyüz and Ata 2008; De Groot 2013)

Very high sensitizing capacity of *p*-phenylenediamine
High (>6 %) to very high (>25 %) concentrations of PPD in some commercial and "natural" henna samples
Long duration of contact with the skin
Lack of a neutralizing (oxidizing) agent (as used in hair dyeing)
Presence of oils or solvents (possibly)
Warm skin (tattoos are usually applied in countries with a warm climate) enhances percutaneous penetration of (allergenic) chemicals
Promotion of penetration by the use of syringes damaging the stratum corneum
Promotion of penetration by the use of occlusive dressings for keeping the henna stuck on the skin
Reexposure to the allergen from retouching the tattoo when it starts to fade (usually after 1–2 weeks)

In the great majority, PPD is the sensitizer in black henna tattoo. However, primary sensitization in some patients to related chemicals such as *m*-aminophenol, *p*-aminophenol (which often co-react to PPD, usually interpreted as cross-reactivity to PPD), or other aromatic amines, which have been identified in tattoo materials (Akyüz and Ata 2008), cannot be excluded (De Groot 2013).

Clinical Picture

About 80 % of the patients reacting to a black henna tattoo have the typical clinical picture of acute allergic contact dermatitis with erythema, edema, papules, vesicles, and – not infrequently – bullae. The first signs develop within 1–3 days after applying the tattoo in those already allergic to PPD, to 4–14 days in patients who become sensitized from the tattoo itself. The dermatitis is usually limited to the site of the tattoo in its geometric pattern (Fig. 1), but generalization may occur (Spornraft-Ragaller et al. 2012).

Atypical manifestations include lichenoid contact dermatitis (Chung et al. 2002; Schultz and Mahler 2002) and erythema multiforme-like

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Contact Allergy to Black Henna Tattoos, Fig. 1 Acute vesicular allergic contact dermatitis on the hand of a child. The lesions are limited to the black henna component of the tattoo (the blue-black lines), whereas the *reddish-brown centers*, painted with red henna, are unaffected (Courtesy Esther J. van Zuuren MD, Leiden, The Netherlands)

Contact Allergy to Black Henna Tattoos, Fig. 2 Post-inflammatory hypopigmentation in the form of the tattoo after healing of the dermatitis (Courtesy Esther J. van Zuuren MD, Leiden, The Netherlands)

contact dermatitis (Jappe et al. 2001; Spornraft-Ragaller et al. 2012). There have been serious reactions with lymphadenopathy and fever; some patients had to be admitted to hospital (Spornraft-Ragaller et al. 2012).

Post-inflammatory pigment disorders after healing of the dermatitis occur frequently. *Hypo*pigmentation, which may last for more than 6 months, is seen especially in children (Fig. 2) (Schultz and Mahler 2002); a few cases of *de*pigmentation have been observed (Jappe et al. 2001). Long-lasting *hyper*pigmentation occurs mostly in adolescents and adults with skin type III or IV.

Contact Allergy to Black Henna Tattoos, Fig. 3 Acute allergic contact dermatitis from hair dye in the neck and on the ears

Reported cases of hypertrophic or keloidal scarring were mostly unconvincing.

Hand dermatitis from occupational exposure to black henna tattoo material in tattoo artists appears to be rare, possibly because of wearing gloves.

Consequences of Sensitization to Black Henna Tattoo

Sensitization to black henna tattoo results in contact allergy to PPD. PPD (and/or similar dyes) is present in most permanent and semipermanent hair dyes, which explains the allergic reactions patients experience when later dyeing their hair or eyebrows/lashes (Marcoux et al. 2002; Schultz and Mahler 2002; Søsted et al. 2006; Kind et al. 2012; Spornraft-Ragaller et al. 2012). The resulting allergic contact dermatitis may affect the scalp, the face, the eyelids, the ears, the neck, and the trunk (Fig. 3). Serious

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Contact Allergy to Black Henna Tattoos, Table 2 Examples of chemicals that may cross-react to *p*-phenylenediamine (Jappe et al. 2001; Marcoux et al. 2002; Schultz and Mahler 2002; Sachdev 2005; Van den Keybus et al. 2005; DeLeo 2006; Søsted et al. 2006; Kind et al. 2012; Spornraft-Ragaller et al. 2012; De Groot 2013)

Hair dyes	**Oral drugs**
4-Amino-*m*-cresol[a]	4-Aminosalicylic acid (PAS)
m-Aminophenol[a]	Dapsone
p-Aminophenol[a]	Mesalazine (5-aminosalicylic acid)
2,4-Diaminoanisole	Oral antidiabetics (sulfonylurea derivatives)
2-Nitro-*p*-phenylenediamine[a]	Sulfonamides, including:
Toluene-2,5-diamine (*p*-toluenediamine)[a]	Sodium sulfadimidine[a]
Toluene-2,5-diamine sulfate[a]	Sodium sulfamerazine[a]
Other (azo and non-azo) dyes	Sulfaguanidine[a]
Acid yellow 36[a]	**Topical drugs**
p-Aminoazobenzene[a]	Hydroquinone (skin bleaching agent)[a]
Aniline[a]	PABA (sunscreen)
Bismarck brown R[a]	PABA-derived local anesthetics, including:
2,4-Diaminoazobenzene[a]	Benzocaine (ethyl *p*-aminobenzoate)
p-Dimethylaminoazobenzene	Butacaine[a]
Direct orange 34[a]	Butanilicaine[a]
Disperse black 1, 2	Butyl PABA[a]
Disperse blue 1, 3, 7, 35, 106[a], 124[a], 135[a]	Procainamide[a]
Disperse orange 1[a], 3[a], 76	Procaine[a]
Disperse red 1[a], 17[a]	Parabens (preservatives)
Disperse yellow 3[a], 4, 9[a], 39	Sulfanilamide[a]
Naphthol AS	
Pyrogallol[a]	
PPD derivatives used in rubber	
N-Cyclohexyl-*N*′-phenyl-*p*-phenylenediamine[a]	
4,4′-Diaminodiphenylmethane[a]	
N,*N*′-Diphenyl-*p*-phenylenediamine[a]	
N-Isopropyl-*N*′-phenyl-*p*-phenylenediamine[a]	
N-Phenyl-*p*-phenylenediamine[a]	

Chemicals indicated with [a] have given positive patch tests in patients with an allergic PPD-induced tattoo reaction. These reactions may or may not have been the result of cross-reactivity to PPD. All other chemicals in this table have been observed as giving positive patch tests in PPD-hypersensitive individuals, in whom the PPD sensitization was caused by any source other than a black henna tattoo (e.g., from hair dyeing)

reactions with oozing vesicular dermatitis and massive edema of the face (sometimes the eyes are completely shut) have been observed, especially in children who frequently need to be admitted to the hospital (Søsted et al. 2006).

PPD may also be present in leather, fur, textile, nylon stockings, rubber (Hald et al. 2013), paints, photographic developers, various industrial printing inks, and other products, contact with which needs to be avoided. This may have implications for work and, especially in children, career prospects. For example, the choice for a career in hairdressing would be unwise, but also in occupations such as printer, furrier, shoe shop assistant, and chemistry worker and occupations in the leather, rubber, and textile manufacturing industries and several other jobs, PPD allergic patients may develop allergic contact dermatitis.

Sensitization to PPD from contact with black henna tattoos or other PPD-containing sources also frequently leads to contact allergy to one or more structurally related compounds (which results from cross-reactivity), notably to other

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hair dyes, azo dyes used in textiles, non-azo dyes, rubber chemicals, and a number of topical and oral drugs. The frequency in which this occurs is dependent on the chemical and ranges from infrequent to more than 90 %. In some cases, contact with these compounds may cause later episodes of contact dermatitis or (in the case of allergy to oral drugs) systemic contact dermatitis. Chemicals that are known to sometimes cross-react to PPD are listed in Table 2.

Diagnosis

The diagnosis is suspected on the basis of the case history or the clinical picture and is ideally confirmed by a positive patch test to PPD, which is present in the European baseline series for routine patch testing.

Often, strong to extreme (bullous) patch test reactions to the standard test concentration of 1 % in petrolatum are observed (Spornraft-Ragaller et al. 2011). Therefore, it has been advised to start patch testing with a concentration of 0.01–0.05 % and increase the concentration in case of a negative result (Spornraft-Ragaller et al. 2012).

Patch testing with the causative henna preparation itself is discouraged because of the risk of very strong patch test reactions and possibly active sensitization, in which case the patient was not yet allergic to PPD but becomes sensitized to it by the patch test.

In a few patients, the patch test reaction to PPD is negative, and the causative allergen remains unknown.

Management

Mild allergic reactions require no therapy. In more serious reactions, topical and sometimes oral corticosteroids may be helpful. In exceptional cases, patients may need to be hospitalized (Spornraft-Ragaller et al. 2012).

Despite adequate therapeutic measures, it not infrequently takes several weeks before the eruption subsides. Temporary (sometimes long-lasting) post-inflammatory pigment alterations (hypopigmentation in children, hyperpigmentation in adolescents and adults) are frequent.

Confirmation of the diagnosis by patch testing with PPD (and preferably a number of possibly cross-reacting chemicals to assess the extent of cross-reactivity and identify chemicals that need to be avoided) is advised to aid management. Patients who have suffered from allergic tattoo reactions and who are allergic to PPD are instructed to avoid contact with (products containing) PPD and (possibly) cross-reacting chemicals (Table 2). Career counseling (and sometimes a career switch) may be necessary.

Cross-References

- ▶ Allergen Avoidance: Avoidance Strategies for Skin Allergies
- ▶ Allergens in Gloves
- ▶ Allergic Contact Dermatitis
- ▶ Contact Dermatitis due to Topical Drugs
- ▶ Contact Dermatitis in Children
- ▶ Hairdressers' Occupational Skin Disease
- ▶ Oral Corticosteroids
- ▶ p-Phenylenediamine Occupational Contact Dermatitis
- ▶ Textile Allergy
- ▶ Topical Corticosteroids

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Contact Allergy to Epoxy Resins

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Synonyms

2,2-bis(4-glycidyloxyphenyl)propane; 4,4'-Isopropylidenediphenol-epichlorohydrin; 4,4'-isopropylidenediphenol diglycidyl ether; DGEBA epoxy resin; Diglycidyl; Diglycidyl bisphenol A; Diglycidyl ether of bisphenol A; Diomethane diglycidyl ether; Diphenylolpropane ether; Epichlorohydrin; Epoxy resins

Definition

Epoxy resins (ERs) are among the most widely used types of polymeric systems. ERs are strong skin sensitizers that are a frequent cause of allergic contact dermatitis.

Introduction

ERs are commonly found in industry and at home, as they are extremely versatile. Depending on the final chemical structure, it is possible to obtain hardness, chemical resistance, flexibility, high adhesive strength, good heat resistance, and high electrical resistance. They can be used in adhesives, paints and coatings, sealants, inks, fillers, reinforced polymer composites, and varnishes and have been used in such industries as construction, automotive, aerospace, medical, electronics, offshore, and engineering.

ERs, or ethoxylins, contain at least two epoxy groups formed by two carbon and three hydrogen molecules in a ring and one oxygen atom outside. Epoxy is a Greek word meaning "oxygen out."

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The majority of ERs (75–90 %) are based on diglycidyl ether of bisphenol A (DGEBA), formed by combining epichlorohydrin and bisphenol A.

The epoxy resin systems (ERS) are a mix of ERs with curing agents (hardeners), modifiers, and additives such as diluents, fillers, resinous modifiers, plasticizers, and pigments. All of them can be used during the manufacturing process or in the use of ERS.

The most common contact allergen in ERS is the base resin DGEBA, but other allergens include curing agents, diluents, fillers, and other modifiers.

During the manufacturing process, ERs can vary in average of molecular weight (MW) by polymerization. The low MW ERs (<900 MW) are liquid or semisolid and rich in monomer DGEBA (MW 340). Resins with MW greater than 900 are solids but may contain more than 15 % monomer DGEBA. Low MW ERs have higher sensitizing power than ERs with greater MW.

When there is a requirement for a change in properties or improvement in chemical and physical resistance (e.g., hardness or better flame retardance), epoxy compounds other than DGEBA, such as diglycidyl ether of tetrabromobisphenol A (4Br-DGEBA), tetraglycidyl-4,4'-methylene dianiline (TGMDA), triglycidyl *p*-aminophenol (TGPAP), *o*-diglycidyl phthalate, bisphenol F (DGEBF), glycerol, ethylene glycol, pentaerythritol, and trimethylolpropane, can be used and can be mixed with DGEBA resins.

Skin Sensitization of ERS and Their Main Constituents

Base Resins

The most common contact allergen in ERS is DGEBA. Lower MW ER has the highest sensitization power.

The sensitizing capacity of ERs decreases as the average MW increases. It has been shown experimentally that elevated curing temperature was more effective in reducing the DGEBA concentration than simply waiting until the next day (Hansson 1994). When DGEBA resins are cured at room temperature, the amounts of unreacted DGEBA decrease rapidly in the first 2 days, but thereafter the decrease is slow (Johansen et al. 2010).

Sensitizations due to epichlorohydrin and bisphenol A have been reported but are uncommon. The majority of cases of sensitization to epichlorohydrin occurred in epoxy resins plants (Tavakoli 2003). In the finished DGEBA resins, the proportion of free epichlorohydrin is less than 0.001 %, and the bisphenol A is even smaller. The cases of sensitization to bisphenol A are controversial but were related to photosensitivity cases (Tavakoli 2003; Kwok et al. 2013).

Non-DGEBA Resins

Contact allergy has been reported from non-DGBA ER but is infrequent (Tavakoli 2003; Conde-Salazar and Ancona 2000).

Epoxy Acrylates

The binding of ERs to acrylic acid leads to epoxy acrylates or vinyl esters. The best known is the Bis-GMA. They present high retractibility during the hardening process. They are used in dental fillings, photosensitive paints, corrosion-resistant insulation, and electrical insulation and in some applications in the shipbuilding industry. Despite the increasing use of epoxy acrylates, there have been few reports of contact allergy. These have occurred mainly in dental nursing and the ultraviolet light printing industry (Kanerva et al. 1989; Jolanki et al. 1995; Kanerva et al. 2000).

Curing Agents

Hardeners or curing agents cause ERs to interlock to form three-dimensional insoluble structures. The cure may be accomplished with a wide range of temperatures (e.g., 3 °C in seawater to 200 °C in electronic applications). The majority of high MW ERs require hot temperatures for the curing process (thermal curing), and the low MW ERs cure at room temperature (cold curing). The hardeners used in cold curing are mostly polyamines,

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aliphatic and cycloaliphatic polyamides, and isocyanates. Those used for thermal curing are carboxylic acids and anhydrides, aromatic polyamides, and aldehyde condensation products.

The time required for curing is called pot-life and is variable for each ER. Polymerization of an ER starts when the ER contacts the hardener, but accelerators (e.g., tertiary amines) can be added to speed up the polymerization. In ERs used in two-part systems, the curing agents are added to the resins immediately before the application; crosslinking then begins.

Among industrial workers, 30 % had contact dermatitis exclusively to at least one hardener (Johansen et al. 2010).

Among hardeners, polyamines have irritating and sensitizing effects to skin and respiratory tract (Tavakoli 2003).

Modifier Agents

Modifiers or additives are incorporated to provide flexibility or viscosity and to increase strength or hardness. The most important are colorants, fillers, and diluents. Colorants include titanium dioxide (white), carbon black (black), inorganic pigments (iron, cadmium, chromium), and organic pigments (anthraquinone, nigrosin). Fillers include fiberglass, carbon fibers, clay, calcium carbonate, and copper.

Reactive diluents are the most import modifier agents. They are used mainly for reducing the ER's viscosity. They are usually epoxy compounds (glycidyl ethers or glycidyl esters). There are other diluents that are non-epoxy compounds (lactone, tetrahydrofuran). Most reactive diluents are used in the cold-curing process and are blended with commercial epoxy resin at a concentration of 10–30 % (Johansen et al. 2010). They are irritating and have sensitizing capacity, especially the epoxy compound diluents. They are more volatile than DGEBA resins and may cause an airborne dermatitis (Tavakoli 2003).

Contact Allergy

Although the number of sensitized ERs is high, the exact number is difficult to identify because, in many cases, the allergic sensitizations of irritant dermatitis are not separated (Conde-Salazar and Ancona 2000). ERs have been found to be one of the most frequent causes of occupational allergic contact dermatitis (Johansen et al. 2010). The use of ERs has increased in recent years and is expected grow in the future. Furthermore, as demand for a new generation of ERs with improved properties increases, new hardeners, diluents, and epoxy base resins may be introduced with unknown skin sensitization effects.

The highest ER sensitization incidence occurs in industrial workers. Cases have been reported in many occupational settings: electronics, metal working, flooring installation, prefabricated construction, fiberglass binding, and marble working (Tavakoli 2003). ER contact dermatitis is less common outside of industry, but its use is so diverse that it is not unusual for accidental contact or domestic use of ER to cause this type of dermatitis. In fact, a positive patch test to DGEBA can be found in patients where the cause of the allergic dermatitis is unknown.

The construction industry is where the majority of cases have been described. In a study performed in an epoxy-based construction industry, it was found that 16.4 % of the workers had acquired occupational contact allergy to ERs within 1 year of employment (Johansen et al. 2010; Ponten et al. 2004). Another paper reported found 18 % of construction workers exposed to ERs had dermatitis on the hand and/or forearm and 20 % of exposed workers had positive patch tests (Van Putten et al. 1984). This may be because the ERs commonly used in the construction industry are of low MW. As described earlier, the sensitizing capacity of ERs can be decreased in inverse proportion to the increase in the average MW of the resin. In addition, the application of ERs in the construction industry is mostly performed by hand and contamination of the skin may occur easily. Therefore, the construction industry has a higher sensitizing potential compared with other applications that use higher MW ER.

The dermatitis generally affects hands and forearms, but the face (eyelids) and genital area

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may also be involved by transporting the substance via contaminated hands. Cases of airborne exposure and photosensitivity, depigmentation, contact urticaria, and respiratory problems have been reported (Johansen et al. 2010; Tavakoli 2003; Conde-Salazar and Ancona 2000; Higgins and Collins 2012; Hannu et al. 2009; Silvestre et al. 2003).

Diagnosis (Patch Test)

Most cases (60–80 %) of contact dermatitis to ERs are sensitized to DGEBA resin. Patch test with ER 1 % in petrolatum is included in most standard series and allows diagnosis in most cases. However, when contact allergy to others substances is suspected, it is necessary to obtain information and samples from the manufacturer and test the components of the ER separately. There are too many hardeners and diluents on the market for use in routine testing. A patients' own work materials should not be tested unless their composition is known and low concentrations of those substances can be prepared for patch tests, usually no larger than 1 %, and checks carried out in healthy volunteers. The recommended test concentration for hardeners and reactive diluents is 0.1–1 % in petrolatum, acetone, or ethanol (Conde-Salazar and Ancona 2000). Reading of patch tests should be performed at 48 and 96 h. If a reading is performed only at 48 h, approximately 15 % of contact allergies might be missed (Johansen et al. 2010). Table 1 present the ERs' major allergens and their optimal concentrations for patch tests.

Contact Allergy to Epoxy Resins, Table 1 Epoxy resins systems and patch tests (Adapted Conde-Salazar and Ancona 2000)

Base resins	
Epoxy resin, MW 340	1 % pet
Bisphenol A	1 % pet
Epichlorohydrin	1 % pet
Hardeners	
Aliphatic	
Ethylenediamine (EDA)	1 % pet
Diethylenediamine (DETA)	0.5 % pet
Triethylenediamine (TETA)	0.5 % pet
Dipropylenetriamine (DPTA)	1 % pet
Tetraethylenepentamine (TEPA)	1 % pet
Diethylaminopropylamine (DEAPA)	1 % pet
Aromatic amines	
p-p' diaminodiphenylmethane, 0.05 % in petrolatum	0.05 % pet
Cycloaliphatic	
Isophoronediamine, 0.1 % in petrolatum	0.1 % pet
Reactive diluents	
N-butyl glycidyl ether	0.25 % pet
Phenyl glycidyl ether	0.25 % pet
Allyl glycidyl ether	0.25 % pet
Others	
Phthalic anhydride	1 % pet
Maleic anhydride	1 % pet
Triphenol	1 % pet

Prevention of ER Contact Dermatitis

The following measures help to prevent contact dermatitis caused by ERs:

1. **Provide information**: Workers using ERs should be informed of the risk of sensitization and should be advised to refrain from skin contact with ERs. Washing the hands immediately after contamination of the skin is a preventive measure (Johansen et al. 2010). Also, x all contaminated equipment should be cleaned regularly.
2. **Protect and prevent unhealthy skin**: Unhealthy skin, including small abrasions, should be protected from ER exposure because it increases the risk of sensitization. For the same reason, the simultaneous use of irritant chemicals should be avoided.
3. **Personal protective measures**: The use of many types of gloves can reduce exposure to ERs. ERs are able to penetrate plastic and rubber gloves. The best type of recommended gloves for ERs is multilayered plastic gloves (4-H glove, layers of polyethylene bonded to an inner layer of a copolymer of ethylene and vinyl alcohol). Butyl rubber gloves are the second best option (Tavakoli 2003). Although laminated 4-H gloves have been found to be

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the most effective, their use by the construction workers is impractical because of their lack of acceptable mechanical properties like resistance to tears and punctures. The use of some barrier creams has been reported to protect against ERs (Blanken et al. 1987), but their use in some applications, particularly in the construction industry, is often impractical.

4. **Avoiding use of low-ERs**: The use of the ERs MW340 oligomer at the lowest possible concentration and the use of high MW reactive diluents are recommended for reducing development of an allergy.
5. **Promote the use of one-part ERs**: Wherever possible, use of two-part epoxies should be replaced by one-part epoxies as it reduces the risk of skin contact during hand mixing. Contact with incompletely cured resins should be avoided.

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Contact Allergy to Hair Dyes

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Synonyms

Allergic contact dermatitis to hair dye ingredients

Definition

Contact allergy to hair dye ingredients is an inflammatory skin disease caused by skin contact with low-molecular-weight sensitizing hair dye substances in the environment. It is a type IV immunological reaction. Individuals may become sensitized from a single exposure to a hair dye or from a series of exposures over time. Once sensitized, subsequent exposure exceeding a certain threshold level will result in the development of allergic contact dermatitis.

Hair dye allergy may cause severe clinical reactions, with edema of the face, eyelids, and scalp. More moderate reactions are seen as

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erythema, suppuration, and ulceration, typically at the scalp margin and on the ears, and sometimes with evidence of eczema where the dye has run down the neck.

The reaction typically starts two dyes after application of the dye and will typically disappear within a month (Søsted 2007). Among hairdressers, the typical reaction is seen as hand eczema (Lysdal et al. 2011). The only cure for hair dye allergy is to avoid skin exposure to hair dyes.

Introduction

Henna was originally used in ancient Egypt to stain the fingers and toes of the Pharaohs prior to mummification. This goes back 4,000 years, and today, in the twenty-first century, people still color their body and hair. By the end of the nineteenth century, the oxidative hair dye process had been invented. Reactions with aromatic amines, such as paraphenylenediamine (PPD), toluene-2,5-diamine and *m*-aminophenols, resorcinol, and hydrogen peroxide, made it possible to make a permanent coloring of hair (Balzer et al. 2001). Contact dermatitis to synthetic hair dyes has been known for many years, and in 1939, Bonnevie suggested resorcinol, PPD, and aminophenol as part of a patch test standard series for identifying patients sensitized to PPD by furs, hair dyes, or occupational exposure (Bonnevie 1939). Today, PPD still is allowed for the coloring of human hair, and the sales of hair dyes containing aromatic amines are very substantial. A Danish population-based study showed that almost 75 % of women and 18 % of men had dyed their hair at some point in their lives (Søsted et al. 2005). Nowadays about half of population have ever dyed their hair (Orton 2008). But among young Danish females, eight out of ten young have ever dyed their hair and 10 % of these had an allergic eczematous reaction while 3 % had an edema reaction (Bregnhøj et al. 2011). Allergic contact dermatitis has been seen to occur from all kinds of hair dyes (permanent oxidative, semipermanent, and temporary dyes).

Clinical Picture

The severity of clinical symptoms from hair dyeing may vary considerably. There may be intense edema of the face, particularly of the eyes, with exudation of the scalp. Erythema and swelling may extend down the neck, onto the upper chest and arms, and can even become generalized. The swelling of the face may be so striking that a mistaken diagnosis of angioneurotic edema is made (Søsted et al. 2002; Cronin 1980). Less dramatic symptoms are periodic swelling of the eyes related to hair dyeing and acute eczema at the scalp margins, sometimes extending to the neck or face (Bonnevie 1939; Cronin 1980).

Men dyeing their beard may have similar symptoms, also with varying severity (Hsu et al. 2001).

In hairdressers, the most common regions affected are the hands and arms (Frosch et al. 1993); however, even though patients who apply the dye themselves wear gloves, their hands and arms occasionally may be affected (Cronin 1980).

The onset of symptoms may be from a few hours to the following day(s). The symptoms can be long lasting, even though hair dyeing is avoided. In a study concerning 55 cases of hair dye allergy, 23 had symptoms for more than 3 weeks, and hair loss has been reported following severe scalp reactions (Søsted et al. 2002; Aguirre et al. 1994).

A number of morphological variants of disease expression occur, including leukoderma, lichenoid, and erythema multiforme-like rash (Brancaccio et al. 2002; Sharma et al. 1999; Tosti et al. 1987).

Hair dye allergy may cause severe clinical reactions, with edema of the face, eyelids, and scalp. More moderate reactions are seen as erythema, suppuration, and ulceration, typically at the scalp margin and on the ears, and sometimes with evidence of eczema where the dye has run down the neck.

Diagnosis

A key step in the diagnosis of hair dye allergy involves patch testing with commercially available

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screening series of hair dye ingredients for routine investigations or by workup of the individual case by obtaining the exact components in the hair dye from the producer (Søsted et al. 2013).

PPD, a part of the standard patch test and screening trays, and PPD-related substances are commercially available.

Cross-References

- ▶ Allergic Contact Dermatitis
- ▶ Hairdressers' Occupational Skin Disease

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Contact Allergy to Shoe Components

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Synonyms

Footwear dermatitis; Shoe allergic contact dermatitis; Shoe contact eczema; Shoe hypersensitivity reaction

Definition

It is an inflammatory skin reaction due to direct contact with shoe materials which is surrounding the foot.

Introduction

Allergic contact dermatitis of the feet caused by shoe allergens is fairly common and should be

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considered in all patients with chronic foot eczema. Unlike respiratory and food allergies, allergic contact dermatitis is not histamine-mediated but is instead a T-cell-mediated delayed-type hypersensitivity reaction. The basic pathophysiologic process behind these lesions is primary skin contact with an allergenic chemical which triggers an immune cascade and results in an eczematous reaction at the site of contact (Scheman et al. 2008).

Shoe allergy may be acute, subacute, intermittent, or chronic and may appear superimposed on endogenous eczema. Thus, the patient may have more than one diagnosis (e.g., both atopic and contact dermatitises) and more than one culprit allergen (e.g., shoe component plus a topical medicament) (Taylor et al. 2006).

Epidemiology

Data on the prevalence of shoe allergy come from patch test clinics and range from 1.5 % to 11 % (Taylor et al. 2006). The occurrence of shoe dermatitis affects both female and male and all age group, including children. Depending on studies, shoe dermatitis prevalence is similar in both genders, but female predominance seems logical because women between the ages of 20 and 50 often do not wear stockings in the summertime and are thus in direct contact with the potential allergen (Nardelli et al. 2005).

Regarding the causative allergens, studies obtained differences depending on the country where they are committed and the production year because of changes of materials in shoe manufacturing and because this information is often hard to obtain from manufactures. But, in general, the most common shoe components usually involved are p-tertiary butylphenol formaldehyde, potassium dichromate, nickel, rubber chemicals, colophony (rosin), and dyes (Warshaw et al. 2007; Bajaj et al. 2007).

Risk Factors

There are activities and jobs with more risk of developing allergy to shoes. Manufacturing shoe professionals are workers with highest risk of sensitization because of prolonged contact with the materials of the shoe but also military personnel and athletes. Wearing closed shoes for long hours creates a humid environment around the foot.

The moist, occluded environment created by shoes increases the risk of developing allergen sensitization and eventual dermatitis. While socks provide some barrier to chemical exposure, they do not provide complete protection, as chemicals may leach out of the shoe into the sock with continued wear (Jacob and Herro 2013)

Contact dermatitis on the foot is more likely in atopic patients due to a disruption of the cutaneous barrier and it is more likely in warm climates because of humid environment.

Clinical Presentation

Shoe dermatitis usually appears as a bilateral involvement on the dorsa of the feet, toes, or sole in heavy, sparing the flexural creases of the toes and the sides. But it may be patchy and even unilateral. Moreover, in chronic cases, the specific pattern of the disease may no longer be present. For example, allergens can leach out of the shoe to affect parts of the foot that are not normally in contact with it (Nardelli et al. 2005).

Clinical signs can be erythema, papules, vesicles, or blisters, oozing, scaling, and crusting, and, in chronic cases, present hyperpigmentation and lichenification.

The pattern of presentation may hold the clue for the causative material. The most affected areas are the dorsum of the foot and the sole. So, dorsal foot dermatitis points to an allergen in the upper or tongue of the shoe, and plantar foot dermatitis (sparing the instep and flexural creases of the toes) indicates that the allergen is in the insole, the shoe lining, or the adhesive which holds these two layers in place. Besides, chemical materials from heel stiffeners and counters must be taken into account when dermatitis affects the dorsal toes or heels. Finally, hand and foot dermatitis could be simultaneous and not exclude the diagnosis of shoe dermatitis.

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Allergens in Shoes

This section includes some of the most common allergens which cause contact dermatitis and its location (see Table 1).

Leather and shoe dyes were the most common allergens in shoe dermatitis during the 1930s and 1940s. However, chromium compounds, which are used not only as tanning agents for leather but also as dyes for both leather and non-leather synthetic uppers of the shoes, are still the most important shoe allergens in many European countries (Nardelli et al. 2005) and, according to a recent study, also in India. This is in contrast to other parts of the world such as the USA, Canada, Brazil, and Asia, where rubber allergens which became more important since the 1950s are more predominant (Johansen et al. 2010).

Diagnosis, Patch Testing

The diagnosis of shoe contact dermatitis is based on a detailed clinical history including hobbies and occupation of the patients; besides, a differential diagnosis (such as athlete's foot, atopic dermatitis, tinea pedis, juvenile plantar dermatosis, etc.) must be made by observing the type of skin lesions and location. It has to be kept in mind that allergic contact dermatitis can be superimposed on a primary skin disease.

Once lesions are identified, it is recommended a study with patch testing on healthy skin during disease-free intervals to identify the causative agent.

Allergic contact dermatitis is diagnosed by a procedure called patch testing. It is performed by placing standardized concentrations of contact allergens on either aluminum (Finn) or plastic (IQ) chambers and attaching these to the skin of the back with hypoallergenic paper tape, although commercial standard series of patch test exist nowadays. Patches are typically left in place for 48 h and then removed (Scheman et al. 2008). Once removed and avoiding wet back, a second reading (72 h, 96 h, or even 1 week) is made, depending on the clinical case. Reactions are graded as 1 when it is only an erythema; 2 when it is edema, erythema, and discrete vesicles; and grade 3 when it is coalescing vesiculobullous papules.

Regarding application and lecture techniques, some authors recommend to leave the shoe pieces in place for 4 or 5 days (Storrs 1986) or even for a prolonged 14-day exposure, rather than the usual 48 h. And to help replicate the conditions of the shoe wearing, soaking the pieces is suggested (Jordan 1972).

To diagnosis shoe allergic contact dermatitis, first, it is advised to select and carefully prepare pieces of worn shoe to patch. These, sometimes, are positive, but compounds are unknown, and the causative allergen is elusive. Nevertheless, it is still recommended to identify the culprit of dermatitis.

The standard series of patch test (as national or international baseline series or T.R.U.E® TEST panel) include most of relevant allergens from shoe materials, and they will be a great help in the diagnosis process. The simultaneous application of the baseline series can afford a first indication, but further investigation is most often needed.

The next step is to patch test patients with different allergens present in additional series (rubber additives, plastics and glues, textile dyes, etc.) selected according to the recent literature (Johansen et al. 2010).

Other products used in shoe manufacturing must be remembered. Podmore assembled a series of chemicals by breaking down all the constituents of shoes and identifying all possible culprits. These and other lists include resins, rubber accelerators, dyes, plasticizers, tanning agents, antioxidants, and UV stabilizers. Other authors have included p-aminoazobenzene and other dyes; the biocides such as thimerosal, chloroacetamide, and phenylmercuric nitrate; hydroquinone in rubber; vegetable tannins; glutaraldehyde, a rare sensitizer as a leather tannin; polyurethane chemicals (Desmodur, Desmocoll 400, Desmodur R and RF, and dodecyl mercaptan); urethane adhesives; and other adhesive components (Johansen et al. 2010).

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Contact Allergy to Shoe Components, Table 1 Sites of common allergens in shoes (Modified from Johansen et al. 2010)

Allergen	Location	Avoid
Mercaptobenzothiazole	Rubber	Rubber foam uppers + insoles
Tetramethylthiuram disulfide	Neoprene adhesives	Solid rubber shoe soles + heels
	Adhesive + leather treatment biocides	Sock lining adhesives
	Leather finish coats	Fiberboard insoles
		Highly finished leathers
Dibenzothiazyl disulfide	Solid or adhesive neoprene	Sock lining adhesive
(MBT mix)	Rubber	Rubber soles or heels
		Rubber insole sponge
Thiourea	Solid or foam neoprene	EVA-neoprene-nylon combination insole
Diaminodiphenyl methane	Polyurethane	Shiny upper foam
		Combination shoe soles
Colophony	Tackifying resins	Natural rubber latex cement (sock lining adhesive)
		Heel and toe counters
Paratertiary butylphenol formaldehyde resin	Tackifying resin	Neoprene adhesives (sock lining adhesives)
		Heel and toe counters
Nickel	Metal trim	Dimethylglyoxime-positive eyelets
Formaldehyde	Leather tanning	Lutidine-positive leather or soft perspiration-proof leather
	Biocides in natural rubber latex adhesives	
Chromate	Leather tanning	Leather
		Athletic shoe uppers

It is important to have in mind that sometimes, the allergens implicated are topical drug which permeates the shoe and not to forget within patch series.

Dimethyl fumarate, used as an industrial wide-spectrum biocide in Asia and mainly in China, provoked a worldwide epidemic of severe contact dermatitis due, initially, to Chinese sofas. It also induced severe dermatitis and burning due to shoes and contaminated clothing as well. This chemical is present as a white powder or tablets contained in little bags disposed around the materials for protection. It progressively evaporates and therefore contaminates the textiles, although direct contamination is possible. It is forbidden in the European Union (Johansen et al. 2010).

Thus, having detailed information on shoe construction and all component chemicals is a helpful and ideal approach in diagnosing shoe allergy. However, this information is often hard to obtain from manufacturer. In spite of this, the step is crucial for further advice in the choice of alternative shoes (Lachapelle and Maibach 2012).

Differential Diagnosis

In many cases, pathologies overlap, and, for example, allergy contact dermatitis is usually superimposed to hyperhidrosis. Clues that can lead to conclude that these are other diseases may be:

- Infection (tinea pedis): Interdigital dermatitis is more likely.
- Irritant contact dermatitis: Often linked with maceration.

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- Athletic shoe: Dermatitis that involves instep.
- Juvenile plantar dermatosis: Dermatitis only appears on the weight-bearing aspects of the soles in children between 3 and 14 years of age.
- Atopic eczema: Involves the ankle and dorsal first toe.

Other skin pathologies included psoriasis, lichen planus, and dyshidrotic eczema.

Allergic contact dermatitis to topical drugs (topical antibiotics, antihistamines, corticoids, anti-inflammatory, or antimycotics) or cosmetics occurs often, and they appear as an unusual pattern. Medicaments and cosmetics which the patient is using should be included when patch testing (Davis 2009).

A confounding factor is allergy to disperse dyes from socks and stockings. Allergy to various textile dyes has been reported to constitute up to 10 % of foot allergic contact dermatitis (Johansen et al. 2010).

Disperse dyes are the most prevalent causes of textile-related allergic contact dermatitis. They are used for dyeing synthetic fabrics made from fibers composed entirely of polyester, acetate, and nylon or a blend of these with other fiber types; they are not used to dye natural fibers (e.g., wool, cotton, and linen). Disperse dyes do not chemically bond to the fibers, and their small, lipophilic molecules can therefore easily migrate onto the skin of the person who is wearing the garment, especially if the textile fastness is poor; they may be removed by rubbing and by exposure to water (Malinauskiene et al. 2013).

Thus, shoe dermatitis may be imitated by dye from fabrics (both disperse dyes and non-disperse dyes as p-phenylenediamine, a classic textile marker which is not always positive in patch test from fabric allergic patients). A clinical clue to stocking allergy diagnosis is that it may spare the toe webs, while involving the rest of the feet and legs.

Management (Allergen Substitution)

Most of lesions could be treated with topical corticosteroids and intensive hydration, but the definite management is to avoid the offending allergen.

The allergic patient must know the shoe materials and its composition to avoid contact with allergens which cause the problem. However, this can be tricky, as manufacturers do not provide all the products used to prepare the shoe. So, recommendations which can be given to the patient are:

- *Insole allergic patients*: Replace leather soles to cork or felt soles, preventing to stick with glue. Besides, take into account bactericidal products or deodorants added to the rest of the shoe.
- *Other parts of the shoe allergic patients*: Use loafers without insoles or adhesives (sewn or stapled joints), and also use injection-molded plastic shoes or wooden shoes.

If specific allergens are known, take into account the following:

- *Allergy to rubber or leather*: Use vinyl or wood shoes. Replacing the insoles with composition as cork or felt, which is glued in with a non rubber cement or is stapled instead of glued.
- *Allergy to chromium*: Wearing quality leather new shoes; Discarding those that have been used in a few months (to prevent leaching out); and bring extra pairs of socks (cotton, long) (to avoid contact with the allergen). Use, although with controversial indications, hypoallergenic shoes (Taylor et al. 2006). In the event that these recommendations are not sufficient, the patient should replace skin shoes for plastic, fabric shoes (canvas), or clogs (e.g., wooden clogs with vegetable-tanned leather).

These simple measures can, according to certain authors, result in clearance of half the cases of allergic shoe eczema due to an unknown allergen (Nardelli et al. 2005).

Conclusion

Every day, manufacturing shoes is changing. Years ago, the leather and artisan methods dominated, but today manufacturing is increasingly

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mechanized, and new products for adhesion and fixation are used, as well as rubber and synthetic materials, dyes, and metallic or waterproof finishes, not to mention sports shoes which are made to facilitate the exercise.

There are tools which help to approach the problem which causes contact allergy to shoes and to solve it, but further studies are needed.

Cross-References

- Allergic Contact Dermatitis
- Allergen Avoidance: Avoidance Strategies for Skin Allergies
- Cobalt Contact Dermatitis
- Contact Dermatitis Due to Topical Drugs
- Cutaneous Drug Reactions
- Epidemic Contact Dermatitis Due to Dimethyl Fumarate
- Nickel Allergic Contact Dermatitis
- Nickel Contact Dermatitis
- Textile Allergy

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Contact Dermatitis Due to New Metals

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Synonyms

Allergic contact dermatitis due to metals; Allergic eczema due to metals; Metal contact dermatitis; Metal sensitivities

Definition

Metal contact dermatitis is a skin inflammatory reaction by direct exposure of metals with the skin in patients who are sensitive to these allergens.

Introduction

Contact dermatitis due to nickel, chromium, and cobalt is the most studied and most prevalent skin allergy. Metal allergy is mainly caused by

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prolonged or repeated skin exposure to metallic items such as jewelry, cell phones, clothing fasteners, and leather goods (Basko-Plluska et al. 2011).

Historical Background

Around 70,000 years ago, copper was used in jewelry. The Egyptians preferred the luxury, rarity, and workability of gold over other metals. Modern fine jewelry usually includes gold, white gold, platinum, palladium, titanium, or silver. Due to the new times and increase of nickel and gold allergy, new alloys and metals have been used.

The use of metallic materials in orthopedic prosthesis and dental implants has become widespread since the middle of the twentieth century. The initial prosthesis had pairs of friction metal producing a great friction and, therefore, the deposit of metallic particles in the tissues of the joint (Gawkrodger 2003). Soon after appeared the first publications suggesting the role of prostheses and implants in the appearance of eczema and hives (Foussereau and Laugier 1966). The high prevalence of contact allergy to these common metals, as well as the search of new functional or aesthetic properties, has forced the use of new metals and alloys not only for medical uses (intracoronary stents, prosthesis valves, endovascular prostheses, gynecologic devices) but also for recreational uses. That means that many unusual metals and alloys can nowadays be in contact with the skin and other body surfaces. These metals have also demonstrated their capacity to react with the immune system and develop allergic contact dermatitis (García Abujeta et al. 2004).

Prevalence

Metal hypersensitivity is not uncommon. About 10–15 % of the population is sensitive to metals. Nickel is the most common metal sensitizer in humans, especially in women due to use of jewelry. Cobalt and chromium are the next most common metal sensitizers. The frequency of contact allergy to gold was reported to be 5–10 % in patch-tested patients with eczema (Bruze and Andersen 1999). The frequency of **palladium** sensitivity reported in ranges from 5.3 % to 97 % (Filon et al. 2003). **Indium** allergy seems extremely rare (Gamboni et al. 2013).

Pathogenesis

Contact of metals with biological systems provokes corrosion, due to mechanical wear, as well as other physiochemical factors and thus the release of ions that can activate the immune system by forming metal-protein complexes capable of eliciting hypersensitivity responses (Bruze and Andersen 1999).

The amount of metals released due to corrosion is relatively low (around 11 mg/year for a hip prosthesis), but it is a factor that contributes to the accumulation of metal. However, the total number of metal ions released by corrosion is half of the calculated as necessary for nickel to sensitize through the skin, so their pathogenic significance is controversial (Merrit and Brown 1996). Independent of the mechanism involved in metal ion release, metal ion exposure may result in activation of macrophages and delayed-type hypersensitivity.

New Metals

In Table 1 there is a resume of the different new metals, their source of exposition, and the reported cases of relevant allergic reactions.

Modern **stainless steel** used in implants have very low **zinc** content and contain 13–16 % nickel, 17–19 % chromium, and 2–4 % **molybdenum** (Hallab et al. 2001). It is used in dental implants, orthopedic implants, and endovascular devices.

Titanium is a material more biocompatible (Schliephake et al. 1993), but less hard than nickel, chromium, and cobalt. It is usually considered a safe alternative in patients with a history of reactions to metals that require fixation of fractures. It is also used in jewelry, in tattoos, and in medical devices such as

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Contact Dermatitis Due to New Metals, Table 1 New metals: uses and allergic contact dermatitis

Metal		Jewelry	Spectacle Frames	Tattoos	Dental	Orthopedic	Pacemaker/stents	Gynecological	Occupational ACD	+ RPT
Be	Beryllium	x			x				Dental mechanic	x
B	Boron	x			x		x			
Mg	Magnesium		x							
Ti	Titanium	x	x	x	x	x	x	x		
V	Vanadium	x			x	x	x		Ceramic	x
Mn	Manganese		x	x	x	x	x	x	Ceramic, metallurgy	x
Zn	Zinc		x		x		x		Gloves	x
Ga	Gallium	x			x					x
Se	Selenium	x								
Sr	Strontium				x					
Yt	Yttrium	x			x					
Zr	Zirconium	x			x	x				
Nb	Niobium	x	x		x	x				
Mo			Molybdenum	x			x	x	x	
Ru	Ruthenium				x					
Rh	Rhodium	x	x		x		x		Metallurgy, goldsmith	x
Pd	Palladium	x	x		x		x		Chemical industry	x
Cd	Cadmium		x	x	x				Ceramic	x
In	Indium	x	x		x					x
Sn	Tin	x			x		x	x	PVC gloves, metallurgy, boat paints	x
Sb	Antimony						x		Ceramic	x
Te	Tellurium	x			x					
Ta	Tantalum	x				x	x			x
W	Tungsten	x			x	x	x			
Ir	Iridium	x	x		x		x	x	Electrochemical factory (contact urticaria), radiologist (radiodermatitis)	x
Pt	Platinum		x		x		x	x	Chemical industry	x
Pb	Lead		x				x			
Yt	Ytterbium				x					

ACD allergic contact dermatitis, *PVC* polyvinyl chloride, *+ RPT*, Positive relevant patch tests

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prostheses, dental implants, and cardiac pacemakers (Schalock et al. 2012). **Nitinol** is an alloy of nickel and titanium often used in endovascular devices and gynecologic implants for contraception. It is also used in aerospace, petrochemical and automotive industries, agriculture, and military activities. It is an uncommon cause of contact dermatitis/sensitization, but has been involved in some cases of rejection to prostheses and pacemakers.

Tantalum is a gray, glossy, ductile, and very hard metal. It is used in the manufacture of electronic devices, jewelry, and pacemakers and prostheses. A case of reaction to a metal prosthesis has been reported (Romaguera and Vilaplana 1995).

Vanadium is a soft, ductile, and not abundant metal and becomes part of some alloys. It is used in jewelry and medical devices. Sensitization to this metal has been related in some cases with loosening of the prosthesis.

Platinum group metals (PGMs) are a group of metals (**palladium**, **platinum**, **rhodium**, **ruthenium**, **iridium** and **osmium**) with similar chemical properties.

Palladium is a lustrous silvery-white metal that has become an important contact allergen (Filon et al. 2003). It is used in electronics, in chemical industries, in jewelry, and in medicine.

Iridium is the most corrosion-resistant metal known so far. It is used in jewelry and dental implants ("white gold"). Individual cases of occupational contact urticaria in an electrochemical factory and radiodermatitis in a radiologist have been reported.

Indium is a soft, silvery-white metal with a luster crystalline. It is extremely ductile and malleable and improves the strength and corrosion resistance of alloys. It is used in thermistors and as thin-film coatings in liquid crystal display screens such as those used in computers and DVD players. Other reported uses include indium-containing alloys amalgamated with mercury to form dental amalgam and radiolabeled isotopes in medical research. It is also used in jewelry as an alternative to nickel-allergic patients. A case of contact dermatitis due to a "hypoallergenic" wedding ring has been reported (Gamboni et al. 2013).

Zinc is a bluish-white, lustrous, diamagnetic metal. A variety of zinc compounds are commonly used, such as zinc carbonate and zinc gluconate (as dietary supplements), zinc chloride (in deodorants), zinc diethyldithiocarbamate (in gloves), zinc pyrithione (anti-dandruff shampoos), zinc sulfide (in luminescent paints), and zinc methyl or zinc diethyl in the organic laboratory. There are described local reactions due to gloves and shampoos and several cases of systemic allergy reactions due to zinc treatments.

Tin is a malleable, ductile, and highly crystalline silvery-white metal. It has long been used as a solder in the form of an alloy with lead. Nowadays, it is used in jewelry and medical devices. There are reported cases of occupational contact allergy due to PVC gloves (di-*N*-octyl) tin-bis (2-ethylhexyl maleate), in metallurgic industry and of airborne dermatitis due to its use in boat painting.

Clinical Manifestations

The period of appearance of the lesions due to prostheses or implants is variable, ranging between the first day and 15 years, while the average between the second and the third year.

Clinical symptoms of allergy to metals are not different of those elicited by other substances in direct contact with the skin. But often new metals are in contact with other parts of the body.

- Eczema (40–47 %) (Dujardin et al. 1995). It often begins in the area adjacent to the implanted material, with subsequent generalization (Kubbar et al. 1981). It is less common to find only a localized eczema.
- Bullous dermatosis (11 %). Usually localized, although a case of severe erythema multiforme and dermatitis herpetiformis has been described. The involvement of the prosthesis in these reaction materials is not

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clear because there is not an affectation located next to these.
- Lichenoid reaction is the most frequent manifestation in dental implants characterized by oral lichen planus-like lesions (Segura-Egea and Bullón-Fernández 2004).
- Inflammatory reactions related with the implants (13 %). Presentation may vary and can be unspecific. In these cases it is important to perform a differential diagnostic with a septic process.
- Other clinical forms. Rashes, urticaria, erythroderma, vasculitis, pigmented fixed exanthemas, etc.

Diagnosis

1. Study of materials

   The knowledge of the metals used is essential. In the case of implants, it should be based on the study of prostheses and implants removed, as well as the surrounding biological material with microbiological (that rating possible infections) and anatomopathological (that assesses reaction of the organism to the implanted material) studies.
2. Patch tests: The commercial batteries of metals (Benson et al. 1975) and methacrylates (Gil-Albarova et al. 1992) are especially useful for the study of reactions to metals due to contact or implants, in addition to the standard batteries used for the study of allergic contact dermatitis.

Prevention

Primary prevention is not feasible. Secondary prevention with avoidance of the known sensitizers is the most effective preventive measure, but nowadays, with the available data, active searching of sensitizations (patch testing or other screening tests) does not seem to be necessary in the candidate population to metal implants.

Management

Symptomatic treatment, usually with topical corticosteroids, identification and avoidance of the offender are the first points of treatment. Systemic corticosteroids may be used depending on intensity of symptoms as well as systemic antihistamines if there is itching.

However, in the cutaneous lesions associated with implanted materials, the attitude must be conservative. The appropriateness of the removal of the materials if lesions persist should be individualized. If replacement of the prosthesis is needed for whatever reason and there is a suspicion of sensitization to the metals implanted, then the use of alternative materials is recommended. The election of the alternative materials needs the use of patch testing with a metal battery.

Conclusion

New metals and alloys are increasingly used in medical devices (dental implants, prostheses, stents, pacemakers. . .). It must take into account other sources of contact with these non-usual metals like users of jewelry, tattoos, and metallic devices or occupational exposure.

Its allergenicity seems low, but its increasing use and the fact that in many cases they are used for implants, favoring a prolonged and tight contact with the immune system, may increase the problem.

For decades, it was believed that only highly susceptible patients (<1 %) developed skin complications due to metal implants; however, the actual figure may be higher (5 %) (Basko-Plluska et al. 2011).

Sensitization to metals would be of relatively little importance as a fundamental cause of rejection of implants, but it could be a contributor to rejection in a greater number of cases. Alternative metal materials normally with better biocompatibility profile also have sensitizing capacity.

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The impact of metal nanoparticles, of increasing importance in the near future, in contact dermatitis to metals has to be studied.

Cross-References

- Allergic Contact Dermatitis
- Aluminum Allergy
- Cobalt Contact Dermatitis
- Gold Contact Dermatitis
- Nickel Allergic Contact Dermatitis
- Nickel Contact Dermatitis
- Oral Antihistamines
- Oral Corticosteroids

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Contact Dermatitis Due to Plants

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Synonyms

Phytodermatitis; Phytophotodermatitis

Definition

Plants are living organisms that humans use to eat (edible plants), to work with them (woods), to apply in natural medicines, and to enjoy in recreational activities (flowers, ornamental plants). In those contexts, contact with plants may cause direct or indirect (airborne) contact dermatitis.

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Contact Dermatitis Due to Plants, Table 1 Plants

Family	Genus	Plant	ACD	ICD	AiD	PhD	ICR	OCD	Occupation
Acanthaceae	*Pachystachys lutea*	Golden shrimp plant, lollipop plant	X					X	Greenhouse gardeners
Alstroemeriaceae	*Bomarea*	Bomarea	X						
Amaranthaceae	*Alternanthera philoxeroides*	Alligator weed				X			
Anacardiaceae	*Comocladia dodonaea* Urban	Christmas bush, poison ash	X						
	Gluta renghas	East coast rengas, ape-nut	X						
	Gluta usitata Ding Hou	Burmese lacquer tree	X						
	Metopium toxiferum	Poisonwood, coral sumac, Florida poison tree	X						
	Rhus coriaria	Rhus, sumac	X						
	Smodingium argutum	African poison ivy	X						
	Toxicodendron	Rush	X						
	Toxicodendron diversilobum	Western poison oak	X						
	Toxicodendron radicans	Poison ivy	X		X			X	Firefighters, foresters, woodsmen, farmers, landscapers
	Toxicodendron rydbergii	Rydberg's poison ivy, Western poison ivy	X						
	Toxicodendron striatum	Manzanillo	X					X	Firefighters, foresters, woodsmen, farmers, landscapers
	Toxicodendron toxicarium	Atlantic poison oak	X						
	Toxicodendron vernix	Poison sumac	X					X	Firefighters, foresters, woodsmen, farmers, landscapers
Apiaceae	*Ammi majus*	Bishop's weed, false bishop				X	CU		
	Angelia sylvestris	Wild angelica, cow parsley				X			
	Angelica archangelica	Angelica, wild celery				X			
	Anthriscus sylvestris	Cow parsley				X			
	Centella asiatica	Centella	X						

(*continued*)

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Contact Dermatitis Due to Plants, Table 1 (continued)

Family	Genus	Plant	ACD	ICD	AiD	PhD	ICR	OCD	Occupation
	Glycyrrhiza glabra	Liquorice, licorice	X						
	Heracleum giganteum	Giant bear claw	X			X			
	Heracleum lanatum	Cow parsnip, masterwort				X			
	Heracleum mantegazzianum	Giant hogweed, hogweed				X			
	Heracleum maximum	Cow parsnip, hogweed	X		X	X		X	Gardeners (using weed eaters)
	Heracleum stevenii	Palm of Tromsø, Persian hogweed				X			
	Psoralea corylifolia	Babchi	X			X		X	
Apocynaceae	*Araujia sericifera*	Moth plant					CU		
Aquifoliaceae	*Ilex*	Holly		X					
Araceae	*Dieffenbachia*	Dumb cane	X	X					
	Philodendron	Philodendron	X	X				X	Nursery, housekeepers
Araliaceae	*Dendropanax trifidus* Makino	Kakuremino	X						
	Panax ginseng	Ginseng	X						
Asparagaceae	*Agave americana*	Century plant, Americana aloe	X	X					
	Drimia maritima	Squill, sea onion	X						
	Ruscus aculeatus	Butcher's broom	X						
	Yucca aloifolia	Yucca	X					X	Gardeners, caretakers of plants
Asteraceae	*Achillea lanulosa*	Yarrow, nosebleed, milfoil	X						
	Ambrosia acanthicarpa	Bur ragweed, sandbur	X						
	Ambrosia artemisiifolia	Ragweed	X		X			X	Gardeners, farmers
	Ambrosia deltoidea	Triangle bur ragweed, Triangle-leaf bursage	X			X			
	Ambrosia psilostachya	Western ragweed, perennial ragweed	X						
	Ambrosia trifida	Giant ragweed, tall ragweed	X						

(*continued*)

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Contact Dermatitis Due to Plants, Table 1 (continued)

Family	Genus	Plant	ACD	ICD	AiD	PhD	ICR	OCD	Occupation
	Anthemis	Dog fennel, mayweed	X			X			
	Anthemis calendula	Capeweed	X						
	Anthemis cotula	Stinking chamomile, corn chamomile	X						
	Arnica montana	Arnica, mountain tobacco	X						
	Artemisia ludoviciana	Dark-leafed mugwort, Prairie sage	X						
	Artemisia vulgaris	Common mugwort	X						
	Bidens	Stickseeds		X					
	Calendula officinalis	Marigold	X						
	Cardus	Thistles		X					
	Cassinia aculeata	Common cassinia, dogwood, cauliflower bush	X						
	Chamaemelum nobile	Roman chamomile, dog fennel	X						
	Cineraria	Cineraria	X					X	Florists, gardeners, housewives
	Cirsium	Thistles		X					
	Conyza bonariensis	Fleabane	X						
	Critonia	Critonia	X						
	Dittrichia graveolens	Stinkwort	X						
	Helenium amarum	Sneezeweed, swamp sunflower		X					
	Helenium autumnale	Sneezeweed, bitterweed		X					
	Inula helenium	Elecampane, horseheal, scabwort		X					
	Iva angustifolia	Narrow-leaf marshelder		X					
	Iva xanthifolia	Marshelder		X					
	Lactuca serriola	Prickly lettuce		X					
	Leucophyta brownii	Cushion bush	X					X	Gardeners
	Matricaria chamomilla	Chamomile, camomile	X		X		CU	X	Forestry workers
	Parthenium argentatum	Guayule	X						

(*continued*)

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Contact Dermatitis Due to Plants, Table 1 (continued)

Family	Genus	Plant	ACD	ICD	AiD	PhD	ICR	OCD	Occupation
	Parthenium hysterophorus	Congress grass, Santa Maria feverfew, whitetop weed	X		X				
	Petasites albus	White butterbur	X						
	Phagnalon rupestre	African fleabane, yesquera	X						
	Saussurea lappa	Costus	X						
	Silybum marianum	Blessed milk-thistle, holy thistle	X						
	Soliva sessilis	Bindi		X					
	Tagetes minuta	Small-flowered stinking roger	X						
	Tanacetum cinerariifolium	Pyrethrum, dalmatian pyrethrum	X						
	Tanacetum parthenium	Feverfew	X						
	Tanacetum vulgare	Tansy, bitter buttons	X						
	Taraxacum officinale	Dandelion, lion's tooth	X		X			X	Gardeners, golfers, farmers, forestry workers, or florists
	Vernonia noveboracensis	New York ironweed	X						
	Xanthium italicum Moretti	Californian burr	X						
	Xanthium spinosum	Spiny cocklebur	X						
	Xanthium strumarium	Noogoora burr	X						
Berberidaceae	*Berberys*	Barberry		X					
Boraginaceae	*Borago*	Borago		X					
	Myosotis	Forget-me-not		X					
	Phacelia crenulata	Phacelia, heliotrope, scorpionweed		X					
	Pulmonaria officinalis	Lungwort		X					
	Symphytum	Comfrey		X					
	Turricula parryi	Poodle-dog bush	X						
	Wigandia caracasana	Caracus wigandia		X					
Brassicaceae	*Sisymbrium officinale*	Hedge mustard					PCD		

(*continued*)

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Contact Dermatitis Due to Plants, Table 1 (continued)

Family	Genus	Plant	ACD	ICD	AiD	PhD	ICR	OCD	Occupation
Burseraceae	*Boswellia serrata*	Boswellia, salai	X						
	Commiphora wightii	Guggul	X						
Caryophyllaceae	*Calophyllum inophyllum*	Alexandrian laurel, batree, laurel wood	X						
	Calophyllum tacamahaca	Tamanu	X						
Cactaceae	*Cephalocereus senilis*	Old man cactus		X					
	Opuntia	Opuntia, nopales	X	X				X	Harvesters, soldiers
	Opuntia ficus-indica	Indian fig opuntia, cactus peak	X						
Cannabaceae	*Cannabis sativa*	Cannabis, hemp					CU		
	Humulus lupulus	Hop	X		X		CU	X	Pickers
Caprifoliaceae	*Lonicera japonica*	Lonicera, Japanese honeysuckle	X						
Chenopodiaceae	*Chenopodium*	Chenopodium, pigweed				X			
	Chenopodium álbum	Lamb's quarters, goosefoot, melde				X			
Cistaceae	*Cistus ladanifer*	Gum rockrose, laudanum	X						
Cornaceae	*Cornus*	Dogwood		X					
Dryopteridaceae	*Arachnoides adiantiformis* Tindale	Leatherleaf, baker fern	X					X	Flower shop workers
Elaeagnaceae	*Elaeagnus angustifolia*	Oleaster, silverberry	X						
Euphorbiaceae	*Croton*	Croton	X	X					
	Euphorbia	Spurge	X	X					
	Euphorbia hermentiana Lemaire	Friendship cactus		X					
	Euphorbia helioscopia	Sun spurge		X					
	Euphorbia lactea	Candelabra cactus		X					
	Euphorbia lathyris	Caper spurge		X					
	Euphorbia marginata	Snow-on-the-mountain		X					
	Euphorbia pulcherrima	Poinsettia	X						
	Euphorbia peplus	Petty spurge		X					

(*continued*)

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Contact Dermatitis Due to Plants, Table 1 (continued)

Family	Genus	Plant	ACD	ICD	AiD	PhD	ICR	OCD	Occupation
	Euphorbia resinifera	Officinal spurge		X					
	Euphorbia tirucalli	Pencil tree		X					
	Euphorbia pulcherrima	Poisenttia		X					
	Euphorbia tirucalli	Pencilbush		X					
	Ricinus communis	Castor oil plant		X			PCD		
	Synadenium grantii	African milk bush		X				X	Gardener
Hypericaceae	*Hypericum perforatum*	St. John's wort	X			X			
Jubulaceae	*Frullania*	Frullania	X		X	X		X	Forestry workers, woodcutters, gardeners
Lamiaceae	*Origanum dictamnus*	Dittany of Crete, hop marjoram	X						
	Plectranthus amboinicus	Country borage, Mexican mint	X						
	Salvia officinalis	Sage, garden sage	X						
Lythraceae	*Lawsonia inermis*	Henna	X				CU		
Meliaceae	Azadirachta indica	Neem, nimtree, Indian lilac	X						
Moraceae	*Ficus benjamina*	Weeping fig	X				CU	X	Gardeners, caretakers of plants
	Ficus pumila	Creeping fig, climbing fig	X						
	Spathiphyllum wallisii	Spathe flower, peace lily	X				PCD, CU	X	Gardeners, caretakers of plants
Papaveraceae	*Bocconia frutescens*	Gordolobo	X		X				
	Chelidonium majus	Greater celandine, wart plant	X	X					
	Meconopsis cambrica	Welsh poppy	X						
	Papaver nudicaule	Iceland poppy	X						
Plantaginaceae	*Plantago*	Plantago	X	X		X			
Proteaceae	*Grevillea*	Grevillea	X					X	Maintenance workers, telephone line workers, woodworkers, gardeners
	Grevillea banksii	Kahili, Bank's grevillea	X						
	Grevillea robusta	Silky oak, silver oak	X						

(*continued*)

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Contact Dermatitis Due to Plants, Table 1 (continued)

Family	Genus	Plant	ACD	ICD	AiD	PhD	ICR	OCD	Occupation
Ranunculaceae	*Caltha palustris*	Yellow marsh marigold, kingcup		X					
	Ceratocephala falcatus	Ceratocephala		X					
	Clematis chinensis Osbeck	Chinese clematis	X						
	Clematis vitalba	Clematis, old man's beard		X					
	Pulsatilla	Prairie crocus		X					
	Pulsatilla vulgaris	Pasque flower		X					
	Ranunculus acris	Meadow buttercup		X					
	Ranunculus falcatus	Ceratocephalus		X					
	Ranunculus constantinopolitanus	Constantine buttercup	X			X			
	Ranunculus damascenus	Buttercup	X			X			
	Ranunculus illyricus	Illyrian buttercup	X			X			
	Ranunculus kotschyi	Ranunculus		X					
Rosaceae	*Prunus spinosa*	Blackthorn		X					
	Pyracantha	Firethorn		X					
	Rosa canina	Rosehip, dog rose		X					
Rubiaceae	*Coffea*	Coffee	X					X	Coffee plant workers
	Galium aparine	Cleavers		X					
	Heterophyllaea pustulata	Cegadera				X			
Rosaceae	*Cotoneaster*	Cotoneaster	X						
Rutaceae	*Cneoridium dumosum*	Bushrue, berryrue				X			
	Dictamnus albus	Gasplant, burning bush, fraxinella				X			
	Melicope anisata	Mokihana		X		X			
	Phebalium argenteum	Australian blister bush				X			
	Ruta chalepensis	Fringed rue				X			
	Ruta graveolens	Rue, herb of grace				X			
Salicaceae	*Salix viminalis*	Osier		X					
Santalaceae	*Santalum*	Chandan, sandalwood	X						
Scrophulariaceae	*Verbascum densiflorum*	Gordolobo	X		X				
	Verbascum thapsus	Flannel plant, wooly mullein		X					

(*continued*)

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Contact Dermatitis Due to Plants, Table 1 (continued)

Family	Genus	Plant	ACD	ICD	AiD	PhD	ICR	OCD	Occupation
Solanaceae	*Nicotiana*	Tobacco	X	X				X	Pickers, Tobacco industry
	Solanum melongena	Eggplant							
Thymelaeaceae	*Daphne*	Daphne		X					
Tiliaceae	*Tilia cordata*	Small-leaved lime	X					X	Cosmetician
Tropaeolaceae	*Tropaeolum*	Nasturtium	X						
Urticaceae	*Laportea canadensis*	Wood nettle		X					
	Urtica dioica	Common nettle, stinging nettle	X	X			CU		
Xanthorrhoeaceae	*Aloe vera*	Aloe vera	X						
Winteraceae	*Pseudowintera colorata*	Pepperwood, mountain horopito	X						

ACD allergy contact dermatitis, *ICD* irritant contact dermatitis, *AiCD* airborne contact dermatitis, *PhD* photodermatitis, *ICR* immediate contact reactions, *CU* contact urticaria, *PCD* protein contact dermatitis, *OCD* occupational contact dermatitis

Contact Dermatitis Due to Plants, Table 2 Trees

Family	Genus	Plant	ACD	ICD	AiCD	PhD	ICR	OCD	Occupation
Anacardiaceae	*Anacardium occidentale*	Cashew nut	X					X	Phenol–formaldehyde resin industry
	Lithraea brasiliensis	Aruera	X						
	Lithraea caustica	Litre	X						
	Lithraea molleoides	Molle	X						
	Myracrodruon urundeuva	Urundeuva	X						
	Schinus terebinthifolius	Brazilian pepper	X						
	Semecarpus anacardium	Marking nut	X					X	Laundry workers, soldiers
	Toxicodendron succedaneum	Rhus tree	X						
	Toxicodendron vernicifluum	Japanese lacquer tree	X					X	Lacquer craftsmen
Annonaceae	*Cananga odorata*	Ylang-ylang	X					X	Manicurists, hairdressers, aromatherapists, cosmetic industry
Apocynaceae	*Aspidosperma*	Brazilian box	X					X	Organists, beauticians
	Dyera costulata	Jelutong	X					X	Woodworkers
Araliaceae	*Dendropanax trifidus*	Ivy tree	X						
	Hedera helix	English ivy, common ivy	X	X					
Betulaceae	*Alnus*	Alder	X						
	Betula	Birch	X						

(*continued*)

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Contact Dermatitis Due to Plants, Table 2 (continued)

Family	Genus	Plant	ACD	ICD	AiCD	PhD	ICR	OCD	Occupation
Bignoniaceae	*Jacaranda*	Jacaranda	X					X	Woodworkers
Combretaceae	*Terminalia superba*	Limba, Afara, Korina					CU		
Cupressaceae	*Calocedrus decurrens*	Incense cedar	X						
	Cryptomeria	Japanese cedar	X		X				
	Cryptomeria japonica	Japanese cedar	X		X				
	Cupressus × *leylandii*	Leyland cypress	X						
	Diospyros celebica	Macassar ebony	X					X	Furniture workers, musicians
	Thuja plicata	Western red cedar	X			X		X	Sawmillers, construction workers, boat makers
Ebenaceae	*Diospyros celebica*	Macassar	X						
	Diospyros crassiflora	African ebony	X						
	Hevea brasiliensis	Rubber tree	X		X		CU		
Euphorbiaceae	*Brya ebenus*	Cocus (wood), granadilla	X					X	Musicians
Euphorbiaceae	*Hippomane mancinella*	Manchineel tree		X					
Fabaceae	*Acacia koa*	Koa	X					X	Woodworkers
	Acacia melanoxylon	Australian blackwood	X		X			X	Foresters, sawmillers, carpenters
	Apuleia leiocarpa	Grapia	X		X			X	Construction
	Bobgunnia madagascariensis	Snake bean plant	X		X				
	Bowdichia nitida	Black sucupira	X					X	Joiners, flooring workers
	Caesalpinia ferrea	Pao ferro	X					X	Furniture workers, guitar maker
	Dalbergia latifolia	East Indian rosewood	X		X			X	Wood turner, furniture makers
	Dalbergia melanoxylon	African blackwood, grenadil	X					X	Musician
	Dalbergia nigra	Brazilian rosewood, Rio Palisander, Obuina	X						
	Dalbergia retusa	Rosewood, cocobolo	X		X			X	Knife handle makers, woodworkers, musicians
	Diplotropis purpurea	Sucupira	X						
	Distemonanthus benthamianus	Ayan, movingui	X					X	Floor workers, woodworkers
	Guibourtia	Bubinga	X						

(*continued*)

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Contact Dermatitis Due to Plants, Table 2 (continued)

Family	Genus	Plant	ACD	ICD	AiCD	PhD	ICR	OCD	Occupation
	Juglans major	Walnut	X						Woodworkers
	Machaerium scleroxylon	Caviuna vermelha	X		X				
	Machaerium acutifolium	Jacaranda	X						
	Millettia laurentii	Wengé	X						
	Millettia stuhlmanii	Panga-panga	X						
	Myroxylon balsamum pereirae	Peru balsam	X			X			
	Peltogyne	Purpleheart	X						
	Pericopsis elata	Afrormosia, kokrodua	X						
	Plathymenia foliusa	Vinhático	X						
	Pterocarpus soyauxii	African red padauk, coralwood	X		X			X	Knife makers, woodworkers
	Vatairea	Faveira amargosa	X		X			X	Woodworkers
Fagaceae	*Fagus*	Beech	X						
Juglandaceae	*Juglans regia*	Persian walnut	X						
	Tectona grandis	Teak	X				CU	X	Woodworkers
Lamiaceae	*Triplochiton scleroxylon*	Obeche, abachi, samba	X		X		CU	X	Woodworkers
Malvaceae	*Mansonia altissima*	Mansonia, bete	X						
	Thespesia populnea	Polynesian rosewood, milowood	X						
Meliaceae	*Azadirachta indica*	Neem, nimtree, Indian lilac	X						
	Entandrophragma	Sipo	X						
	Entandrophragma cylindricum	Sapele					CU	X	Woodworkers
	Khaya anthotheca	Krala	X						
	Khaya ivorensis	Khaya mahogany	X						
	Khaya senegalensis	Senegal mahogany	X						
	Melaleuca alternifolia	Narrow-leaved paperbark	X						
	Swietenia macrophylla	American mahogany	X					X	Furniture workers
Moraceae	*Brosimum alicastrum*	Capomo	X			X			
	Ficus carica	Fig	X			X			
	Milicia excelsa	Iroko, African tea, kambala	X					X	Construction workers, musicians

(*continued*)

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Contact Dermatitis Due to Plants, Table 2 (continued)

Family	Genus	Plant	ACD	ICD	AiCD	PhD	ICR	OCD	Occupation
Myrtaceae	*Eucalyptus*	Eucalyptus	X						
	Eucalyptus pulverulenta	Silver-leaved mountain gum	X		X			X	Florist
	Leptospermum scoparium	Manuka, tea tree	X						
Oleaceae	*Fraxinus americana*	White ash, American ash	X						
	Olea europaea	Olive tree					CU		
Pinaceae	*Abies*	Firs	X						
	Larix	Larch					CU		
	Picea	Spruce	X		X				
	Pinus radiata	Radiata pine	X		X			X	Forestry, wood workers
	Pinus roxburghii	Chir pine	X		X			X	Wood sawyer
Proteaceae	*Grevillea*	Grevillea	X					X	Maintenance workers, telephone line workers, woodworkers
	Grevillea robusta	Silky oak	X						
Rosaceae	*Sorbus aucuparia*	Rowan	X						
Salicaceae	*Populus*	Poplar, populus	X					X	Tree surgeons
	Populus trema	Aspen	X						
	Salix caprea	Goat willow	X						
	Salix phylicifolia	Willow	X						
Sapindaceae	*Lepisanthes alata*	Perupok	X						
Sapotaceae	*Manilkara bidentata*	Manilkara	X					X	Carpenter
	Tieghemella africana	Makoré	X						
Simaroubaceae	*Ailanthus altissima*	Tree of heaven	X					X	Tree surgeons
Thymelaeaceae	*Gonystylus*	Ramin					CU		

ACD allergy contact dermatitis, *ICD* irritant contact dermatitis, *AiCD* airborne contact dermatitis, *PhD* photodermatitis, *ICR* immediate contact reactions, *CU* contact urticaria, *PCD* protein contact dermatitis, *OCD* occupational contact dermatitis

Introduction

Taxonomy of plants is a confusing theme (Botanical Dermatology Database; Solis et al. 2000): changes in the names of family and genus, different plants with the same name, and different names in different countries.

In the tables, there are different lists of plants which have been involved with dermatitis in humans (Le Coz 2011; Zug and Marks 1999): plants (Table 1), trees (Table 2), vegetable foods (Table 3), and flowers (Table 4).

Clinical Manifestations

Plants may cause irritant and/or allergic cutaneous reactions (Pathak 1986; Modi et al. 2009). In most of the cases, hands are the usual affected areas, but other areas may be involved:

- Face and neck due to airborne exposition (e.g., dust wood in woodworkers) (Santos and Goossens 2007)
- Arms and legs due to airborne exposition (e.g., "weed eaters" or "trimmers" dermatitis in gardeners using string trimmers to clear long grass) (Oakley et al. 1986)

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Contact Dermatitis Due to Plants, Table 3 Vegetable foods

FAMILY	Genus	Plant	ACD	ICD	AiCD	PhD	ICR	OCD	Occupation
Cereals									
Poaceae	*Avena sativa*	Oat	X				CU		
	Hordeum vulgare	Barley		X					
	Oryza	Rice					CU		
	Triticum	Wheat	X				CU, PCD		
	Zea mays	Corn					CU		
Dried Fruits									
Anacardiaceae	*Anacardium occidentale*	Cashew nut	X		X			X	Pickers
Betulaceae	*Corylus avellana*	Hazelnut					PCD		
Fabaceae	*Arachis hypogaea*	Peanut					PCD		
Fagaceae	*Castanea*	Chestnut	X						
Jungladeaceae	*Carya illinoensis*	Pecan	X				PCD		
	Juglans major	Walnut		X			CU	X	Bakers
Rosaceae	*Prunus amygdalus*	Almond					PCD		
Fruits									
Actinidiaceae	*Actinidia*	Kiwi	X				CU, PCD		
Anacardiaceae	*Mangifera*	Mango	X				CU		
Anacardiaceae	*Semecarpus anacardium*	Bhallataka, marking nut	X						
Bromeliceae	*Ananas comosus*	Pineapple		X			PCD		
Curcubitaceae	*Citrullus lanatus*	Watermelon					CU		
Ginkgoaceae	*Ginkgo biloba*	Ginkgo biloba	X						
Moraceae	*Artocarpus altilis*	Breadfruit				X			
	Ficus carica	Fig		X			PCD		
	Morus	Mulberry		X					
Musaceae	*Musa*	Banana					CU, PCD		
Myrtaceae	*Psidium guajava*	Guava	X						
Oleaceae	*Olea europaea*	Olive	X				CU	X	Masseurs, pizza makers
Rutaceae	*Citrus aurantifolia*	Lime	X			X	CU	X	Foods handlers
	Citrus bergamia	Bergamot orange	X			X		X	Aromatherapists
	Citrus limetta	Sweet lemon				X			
	Citrus medica	Citron	X			X			
	Citrus paradisi	Grapefruit				X			
	Citrus sinensis	Sweet orange				X	CU		

(*continued*)

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Contact Dermatitis Due to Plants, Table 3 (continued)

FAMILY	Genus	Plant	ACD	ICD	AiCD	PhD	ICR	OCD	Occupation
	Citrus tangerina	Tangerine	X			X		X	Foods handlers
	Citrus x limon	Lemon	X			X	CU, PCD	X	Foods handlers
	Citrus x sinensis	Orange	X			X	CU	X	Foods handlers
Rosaceae	*Malus domestica*	Apple					CU		
	Prunus persica	Peach					CU		
Legumes									
Fabaceae	*Glycine max*	Soybean	X				CU		
	Phaseolus coccineus	Runner bean					CU		
	Phaseolus vulgaris	Common beans	X					X	Farmers
	Vigna	Beans					CU, PCD		
Spices									
Apiaceae	*Anethum graveolens*	Dill					CU, PCD	X	Housewives
	Carum carvi	Caraway					PCD		
	Coriandrum sativum	Coriander					PCD	X	Cooks
	Cuminun cyminun	Cumin					CU		
	Foeniculum vulgare	Fennel				X			
	Petroselinum crispum	Parsley	X			X	PCD	X	Market gardeners
Asteracea	*Tagetes patula*	French marigold (tarragon)	X		X			X	Aromatherapists (tarragon)
Brassicaceae	*Brassica nigra*	Black mustard		X			CU		
	Sinapis alba	White mustard	X	X					
Gingivenaceae	*Curcuma longa*	Curcumin					CU		
Iridaceae	*Crocus sativus*	Saffron	X						
Lamiaceae	*Mentha pulegium*	Pennyroyal, squaw mint, mosquito plant	X			X	CU	X	Cooks
	Mentha spicata	Spearmint	X						
	Mentha x piperita	Peppermint	X						
	Ocimum basilicum	Basil	X					X	Packer of herbs
	Origanum marjoram	Marjoram	X						
	Origanum vulgare	Oregano	X						

(*continued*)

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Contact Dermatitis Due to Plants, Table 3 (continued)

FAMILY	Genus	Plant	ACD	ICD	AiCD	PhD	ICR	OCD	Occupation
	Perilla frutescens	Shiso, perilla	X						
	Rosmarinus officinalis	Rosemary	X		X			X	Farmers
	Thymus vulgaris	Thyme	X		X			X	Farmers
Lauraceae	*Cinnamomum camphora*	Cinnamon	X					X	Waiters, bakers
	Cinnamomum cassia	Chinese cinnamomum	X					X	
	Laurus nobilis	Laurel	X		X				
Pedaleaceae	*Sesamum indicum*	Sesame					CU		
Ranunculaceae	*Nigella sativa*	Black cumin	X						
Solanaceae	*Capsicum annuum*	Paprika, sweet pepper		X			CU, PCD		
	Capsicum frutescens	Chilies		X					
Zingiberaceae	*Zingiber mioga*	Myoga, Japanese ginger	X					X	Greenhouse cultivators
Vegetables									
Amaranthaceae	*Spinacia oleraceae*	Spinach					PCD		
Amaryllidaceae	*Allium ampeloprasum*	Leek	X				CU		
	Allium cepa	Onion	X	X			PCD	X	Cooks, housewives
	Allium sativum	Garlic	X	X	X		PCD	X	Cooks, housewives
	Allium schoenoprasum	Chives	X	X			PCD		
Asparagaceae	*Asparagus officinalis*	Asparagus	X				CU, PCD	X	Pickers, canners, and vegetable cooks
Apiaceae	*Apium graveolens var. dulce*	Celery	X			X	CU, PCD	X	Pickers, canners, and food store workers
	Daucus carota	Carrot	X			X	CU, PCD		
	Pastinaca sativa	Parsnip	X			X	CU, PCD	X	Pickers
Asteracea	*Cichorium endivia*	Endives	X				PCD	X	Cooks
	Cichorium intybus	Chicory	X				PCD	X	Cooks
	Cynara cardunculus var. altilis	Cardoon		X					
	Cynara cardunculus var. scolymus	Artichoke	X			X	CU	X	Pickers, market gardeners, and flower arrangers
	Lactuca sativa	Lettuce	X				PCD	X	Food handlers, chefs, market gardeners, supermarket worker

(*continued*)

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Contact Dermatitis Due to Plants, Table 3 (continued)

FAMILY	Genus	Plant	ACD	ICD	AiCD	PhD	ICR	OCD	Occupation
Brassicaceae	*Armoracia rusticana*	Horseradish		X			PCD		
	Brassica oleracea var. Botrytis	Cauliflower					PCD		
	Brassica oleracea var. gemmifera	Brussels sprouts	X						
	Brassica oleracea var. Italica	Broccoli	X	X					
	Brassica rapa	Turnip	X					X	Cooks, pickers
	Eruca sativa	Rucola					PCD	X	Cooks
	Lepidiumus sativum	Cress					PCD		
	Raphanus sativus	Radish		X			PCD	X	Cooks
	Raphanus sativus var. capitata	Cabbages	X					X	Cooks
	Wasabia japonica	Wasabi		X					
Caparaceae	*Capparis spinosa*	Caper		X					
Curcubitaceae	*Cucumis sativus*	Cucumber	X				PCD	X	Cooks
Poligonaceae	Rheum rhabarbarum	Rhubarb		X					
Solanaceae	*Solanum lycopersicum*	Tomato	X				PCD, CU	X	Restaurateur
	Solanum melongena	Eggplant, aubergine	X				PCD		
	Solanum tuberosum	Potato	X				CU, PCD	X	Restaurateur, cooks

ACD allergy contact dermatitis, *ICD* irritant contact dermatitis, *AiCD* airborne contact dermatitis, *PhD* photodermatitis, *ICR* immediate contact reactions, *CU* contact urticaria, *PCD* protein contact dermatitis, *OCD* occupational contact dermatitis

- Face, neck, legs, and arms due to combined action of sun and plants ("phytophotodermatitis") (Pathak 1986; Solis et al. 2000)
- Systemic reactions due to the ingestion of edible plants with previous cutaneous reactions in relation with them
- Localized areas in contact due to topical herbal treatments

Some jobs are more related with those skin reactions (Zug and Marks 1999):

- Woodworkers (trees)
- Gardeners and nursery workers (ornamental plants, flowers) (de Jong et al. 1998; Lamminpaa et al. 1996)
- Herbalists (herbal treatments)
- Cooks, housewives (vegetable foods) (van den Akker et al. 1990)

In some cases, the skin may be affected by contact with vegetable proteins. Protein contact dermatitis and/or contact urticaria are cutaneous diseases frequent in those cases (Amaro and Goossens 2008; Janssens et al. 1995).

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Contact Dermatitis Due to Plants, Table 4 Flowers

Family	Genus	Plant	ACD	ICD	AiCD	PHD	ICR	OCD	Occupation
Alstroemeriaceae	*Alstroemeria aurea*	Peruvian lily	X					X	Gardeners, florists, housewives
Amaryllidaceae	*Narcissus*	Daffodil, narcissus	X					X	Flower industry
	Narcissus jonquilla	Jonquils	X	X					
	Narcissus pseudonarcissus	Trumpet narcissi, Wild daffodil	X						
Apocynaceae	*Ceropegia woodii*	String of hearts, rosary plant	X					X	Gardener
Araceae	*Aster*	Daisy		X					
	Spathiphyllum	Spathe	X					X	Gardeners
	Zantedeschia aethiopica	Calla lily, Arum lily	X						
Asparagaceae	*Hyacinthus*	Hyacinth		X					
Asteraceae	*Calendula officinalis*	Marigold	X					X	Florists
	Chrysanthemum	Chrysanthemum	X		X	X	CU, PCD	X	Horticulturalists, florists, gardeners
	Dahlia variabilis	Dahlia	X						
	Dendranthema	Autumn-flowering chrysanthemum	X						
	Gaillardia pulchella	Showy gaillardia	X						
	Gervera	Gervera					CU	X	Florists
	Helianthus annuus	Sunflower	X		X			X	Farmers
	Leucanthemum vulgare	Marguerite	X						
Boraginaceae	*Turricula parryi*	Turricula, poodle-dog bush	X						
Cleomaceae	*Cleome spinosa*	Spider flower, cleome	X						
Campanulaceae	*Lobelia richardii*	Perennial lobelia		X					
	Trachelium caeruleum	Blue throatwort	X					X	Florists
Geraniaceae	*Geranium*	Geranium	X				CU	X	Growers, gardeners
Hydrangeaceae	*Hydrangea*	Hydrangea, hortensia	X	X				X	Florists, nursery workers, gardeners
Iridaceae	*Iris germanica var. florentina*	German iris	X						
Lamiaceae	*Lavandula*	Lavender	X	X	X			X	Aromatherapists
Liliaceae	*Erythronium dens-canis*	Dogtooth violet	X					X	Growers, florists
	Tulipa	Tulip	X	X				X	Florists
Magnoliaceae	*Michelia lanuginosa*	Magnolia	X						

(*continued*)

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Contact Dermatitis Due to Plants, Table 4 (continued)

Family	Genus	Plant	ACD	ICD	AiCD	PHD	ICR	OCD	Occupation
Orchidaceae	*Cymbidium*	Boat orchid	X					X	Gardeners
	Oncidium	Oncidium	X					X	Gardeners
	Phalaenopsis amabilis	Moth orchid, phall	X					X	Farmers
Paeoniaceae	*Paeonia officinalis*	Peony	X					X	Nursery
Plumbaginaceae	*Limonium tataricum*	Statice					CU		
Primulaceae	*Primula auricula*	Auricula, mountain cowslip	X						
	Primula denticulata	Drumstick primrose	X						
	Primula obconica	Primula	X		X			X	Florists, housewives
Ranunculaceae	*Anemone*	Anemone		X					
	Aquilegia vulgaris	Columbine		X					
	Helleborus niger	Christmas rose, hellebore		X					
Rosaceae	*Rosa centifolia*	Rose	X	X					
Tropaeolaceae	*Tropaeolum*	Nasturtium	X						
Violaceae	*Viola*	Violet	X					X	Florist

ACD allergy contact dermatitis, *ICD* irritant contact dermatitis, *AiCD* airborne contact dermatitis, *PhD* photodermatitis, *ICR* immediate contact reactions, *CU* contact urticaria, *PCD* protein contact dermatitis, *OCD* occupational contact dermatitis

Cross-References

- Allergic Contact Dermatitis
- Allergic Contact Dermatitis from Exotic Woods
- Contact Dermatitis Due to Topical Traditional Chinese Medicine
- Contact Urticaria and Protein Contact Dermatitis (to Asparagus, Cow's Hair, Seafood, Etc.)
- Plants, Allergic Contact Dermatitis From
- Protein Contact Dermatitis

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Contact Dermatitis Due to Thiourea Derivatives

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Synonyms

Dialkyl thioureas allergy

Introduction

Thiourea and its derivatives have been used industrially since the beginning of the twentieth century. Since late 1960s, these substances have been reported as allergens (Dooms-Goossens et al. 1987). Dialkyl thioureas are reagents used in organic synthesis and most commonly in the manufacture of rubber products. At room temperature, thiourea is a white crystalline solid. They are commonly produced by passing liquid hydrogen sulfide in an aqueous bath of calcium cyanamide, which results in the formation of thiourea.

Dialkyl thiourea derivatives include diethylthiourea (DETU), dibutylthiourea (DBTU), diphenylthiourea (DPTU), ethylbutylthiourea (EBTU), and ethylene thiourea (ETU).

DETU is an accelerator for chloroprene rubber and is also used as antidegradant rubber.

DBTU is an activator for terpolymers and natural rubber and an antidegradant for natural rubber latex and thermoplastic styrene-butadiene rubber.

DPTU is an accelerator and activator for neoprene rubber and termopolymers used for rubber products as wet suites, goggles, knee brace, and gloves. Plastics (particularly if containing polymers) may be thermal decomposed when exposed to high temperatures or prolonged heating. To avoid this decomposition, heat stabilizers as DPTU are used in adhesive tape breaking.

They are mainly organic accelerators and the commonest use is in the process of vulcanization in the production of rubber and neoprene than contain chlorine, as well as antioxidants to prevent neoprene from drying and oxidation.

Uses

Neoprene (chloroprene) is a soft flexible synthetic rubber based on polychloroprene polymerized, widely used due to its soft texture and cushioning ability and resistance to fire, oil, and ozone. DETU and DBTU are the main vulcanization accelerators used in the production of neoprene. Neoprene (Anderson 2009) can be found in:

- Athletic shoes
- Orthopedic braces
- Wrist rests and mouse computer
- Gloves
- Prostheses
- Rubber-based automobile products
- Rubber masks
- Rubber orthopedic braces
- Sleep apnea masks
- Slimming suits
- Splints and foot supports
- Swim goggles
- Wet suits
- Clothing for fire fighters
- Straps for continuous positive airway pressure (CPAP) masks

In the USA, Canada, and Asia, rubber allergens are important as shoe allergens due to the footwear style.

Only 0.5 % of thioureas are used globally as accelerators. They have many other industrial uses and are widely found in:

- Adhesive manufacturing
- Anticorrosive agents
- Paint and glue removers
- Pesticides and fungicides
- Photocopy paper (diazo copy paper), as an antioxidant
- Photography, as an antioxidant

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- Extraction of precious metals
- Rubber accelerator and antioxidant (especially neoprene)
- Synthetic resins
- Textile and dye industry
- Polyvinyl chloride (PVC) adhesive tapes
- Plastic phone card thermo coatings
- Anticorrosive agents
- Metal polish dips
- Blueprints and textile patterns

Epidemiology

Thiourea ACD is relatively uncommon: 1 % of MDTU (mixture of diethylthiourea and dibutylthiourea) tested patients yields positive although it has been reported that using only this thiourea mixture will fail to diagnose 25 % of patients (McCleskey and Swerlick 2001).

In a cross-sectional data study from the North American Contact Dermatitis Group (1994–2004) found in 21,898 patients tested with MDTU, 225 (1.0 %) had positive reactions; of these, 173 (76.9 %) were currently relevant, and 29 (17.1 %) were occupationally relevant. The distribution of gender within the group of patients who had MDTU reactions, however, was approximately equal, in contrast to the general "allergic" population, which was predominately female (Warshaw et al. 2008). MDTU has been considered the allergen with the highest relevance rate in the NACDG standard tray.

Footwear products have been the most frequently ones to cause relevant MDTU, and gloves were the most cited cause of occupational allergic contact dermatitis from dialkyl thioureas.

Clinical Features

Thioureas can cause irritant and allergic contact reactions. ACD affected to areas in contact with materials with these substances. In hands, it may be due to propylene gloves, wrists in contact with wrist rest computers, or palms due to mouse computers. Knees and elbows due to neoprene-containing orthopedics joint braces (Romaguera et al. 1988; Liippo et al. 2010) and also waist due to neoprene belts. Eyelid dermatitis may be affected due to indirect contact of hands with eyes (ectopic dermatitis) in people touching papers with thioureas (Geier and Fuchs 1993) or contact direct with swim goggles.

It has been reported that thiourea-induced allergic contact dermatitis may persist in patients for long time, even after its subsequent avoidance (Ikediobi et al. 2002).

DETU and DBTU have been reported to cause photoallergic and airborne contact dermatitis in office workers exposed to thiourea in certain photocopy papers (van der Leun et al. 1977) or cleaner using silver polish (Dooms-Goossens et al. 1988).

Diagnosis

Clinical History

A comprehensive clinical history should be undertaken, with detailed questions about occupational exposure, homework, and hobbies (sport, swimming). Questions about personal protective measures and clothing (neoprene rubber), indirect contact, and seasonal-related contact topics should be covered.

Clinical course (caused or aggravated by the exposure) and photo or airborne exposure are also to be included in the history.

A detailed history from the patient may reveal which thioureas are the more likely suspects. The majority of cases of neoprene contact dermatitis are due to diphenylthiourea (DPTU), dibutylthiourea (DBTU), diethylthiourea (DETU), ethylbutylthiourea (EBTU), and ethylene thiourea (ETU).

Patch Testing

European baseline series does not include the dialkyl thioureas, so the diagnosis depends on clinical suspicion and aimed testing. A mixture of two thiourea chemicals, referred as mixed dialkyl thioureas (MDTU), has been part of the North American Contact Dermatitis Group (NACDG) standard series since 1991. It is a mixture of diethylthiourea (DETU) and dibutylthiourea (DBTU) at 1 % in petrolatum.

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Testing with MDTU mixture should be used for anyone with a suspected rubber allergy, especially from neoprene. Screening with MDTU picks up about 75 % of relevant thiourea reactions. If there is a high suspicion that a thiourea is the cause of a patient's dermatitis, the patient should be tested with a series of thiourea compounds to increase the percentage of relevant reactions. Other available thioureas for patch testing are diethylthiourea 1 % (DETU), diphenylthiourea 1 % (DPTU), dibutylthiourea 1 % (DBTU), thiourea 0.1 %, and thiourea mix 1.5 % (DBTU 0.5, DETU 0.5, and thiourea 0.1).

Cross-reacting between thiourea compounds, although unlikely, is controversial. From a practical point of view, each component should be tested separately.

Thioureas are included in rubber, shoes, and plastic and glue patch testing series.

Testing with own materials has limitations which may occasionally lead to false-negative results. Solid products with suspect of having thioureas (as rubber) can be tested applying as it is, either as a wafer-thin smooth sheet or as finely divide particulate.

Avoidance

Thioureas or derivates may be found in products containing the following names: dibutylthiourea (DBTU), diethylthiourea (DTU), dimethylthiourea (DMTU), diphenylthiourea (DPTU), ethylbutylthiourea (EBTU), ethylene thiourea (ETU), n,n-diethylurea, tetramethylthiuram disulfide, thiocarbamide, thiourea, or isothiourea.

A study shows that the amount of thiourea leached from rubber articles was greater than the patch test elicitation, which may be helpful to manufacturers designing products which do not release allergens in sufficient amounts to cause reactions in consumers.

Avoiding thiourea is not easy. It may be a hidden allergen in shoes. Patients allergic to thiourea may show problems when using solid or foam neoprene in shoes. They should avoid EVA, ethylene vinyl acetate, and neoprene-nylon copolymer, used in insoles as a shock absorber in sports shoes. In this cases polyurethane insoles may be an alternative. Athletic shoes lining from custom shoemakers may be effective.

There are orthopedic supports lining free of neoprene. Insulating braces with leather may also be effective.

If possible, neoprene-free sports equipment should be used. Several companies offer neoprene-free sports equipment (Scheman et al. 2008). Silicone gaskets swim goggles are available.

Conclusions

Allergic contact dermatitis due to thioureas is relatively uncommon, but may be underdiagnosed as they are not part of the baselines patch testing series. Clinicians should consider this diagnosis in patients who are exposed to neoprene.

Patch testing with thiourea chemicals provides a significant contribution to the diagnosis of contact dermatitis in different patient groups.

Cross-References

- ▶ Allergen Avoidance: Avoidance Strategies for Skin Allergies
- ▶ Allergens in Gloves
- ▶ Allergic Contact Dermatitis
- ▶ Contact Allergy to Shoe Components
- ▶ Sensitization and Allergy to Natural Rubber Latex

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Contact Dermatitis Due to Topical Drugs

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Synonyms

Topical drugs: topical medicines, creams, ointments, lotions

Definition

Contact dermatitis due to topical drugs is an inflammatory reaction which occurs after contact of skin or some mucous membranes with an ingredient of a topical medicament.

Introduction

Allergic contact dermatitis (ACD) due to topical drugs is an immunologic delayed hypersensitivity reaction (type IV). Nevertheless, irritant contact dermatitis is the most frequent response, without an immunologic response. Other adverse cutaneous reactions with topical drugs (Brandão and Goossens 2011) are contact urticaria, erythema multiforme, purpuric rash, exanthema, erythroderma, lichenoid eruption, allergic contact granuloma, toxic epidermal necrolysis, photosensitivity reactions, pigmented lesions, etc.

Prevalence

The real incidence is unknown, but its appearance is rising. Excluding high-risk patients like those suffering leg ulcers and others chronic

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dermatitis, prevalence of about 15 % of the general population is expected (Brandão and Goossens 2011; Spring et al. 2012; Butler and Mowad 2013).

In a recent study (Statescu et al. 2011), 89 of 353 patients with ACD had a topical drug in relation with this pathology: antiseptics (35.89 %), NAIDS (17.94 %), antibiotics (15.39 %), and topical corticosteroids (15.39 %).

Clinical Picture of ACD

ACD to topical drugs is an immunologic reaction in previous sensitized individuals. It is usually an iatrogenic disease induced by topical treatments, but it may also occur as an occupational disease in pharmaceutical industrial personnel, veterinaries and farmers, health personnel (Brandão and Goossens 2011), and other people caregivers (Gacías et al. 2013). The clinical presentation is an eczema like other cases of delayed-type IV hypersensitivity response to exogenous agents. Therefore, ACD due to topical drugs sometimes has certain particularities.

Many factors can play a role in the elicitation of ACD besides the individual predisposition and the inherent sensitization potential of each chemical. Age, sex, environment, and prescribing habits in each country, dose, and concentration are the most important. Some types of vehicles increase skin penetration favoring their irritant and sensitizing capacities and sometimes are impurities, contaminants, and degradation products which may act like a real allergenic material. Damage to the skin barrier is another important contributing contact allergy factor. Patients suffering from a long-term cutaneous disease have a higher risk of sensitization because the exposition to multiple topical preparations over a long period of time increases the probability of developing chronic ACD. Patients with leg ulcers and stasis dermatitis are known to have a very high incidence of topical drug allergy to antibiotics and modern wound treatments like hydrocolloids. Also patients with external otitis, eye problems, perianal and vulvar dermatitis, and chronic hand and foot dermatitis are known to frequently develop secondary medicament contact allergy. There is no consensus about high risk of ACD in patients with atopic dermatitis (Mailhol et al. 2009) or psoriasis when compared with general population, but, nowadays, it is accepted that in atopic children, antiseptic and emollients appear to be the most frequent sensitizers.

Clinical presentation varied case to case. It may present like an acute eczema localized on the site of application of the drug, ranging from a mild erythema to intensely reaction with edematous papules, exudative vesicles, and plaques and scaling in recovering phase. Intense itching is present. There are also cases of acute contact photoallergy (typical described by NSAIDs or neuroleptics) or airborne dermatitis. Acute systemic dermatitis and photodermatitis have been described.

Acute ACD to topical drugs is usually easy to suspect by the existence of vesicle lesions which are rarely seen in chronic presentations with indurated plaques or lichenification. Chronic ACD is the result of the application over prolonged period of time of one or several sensitizer agents. Thus, ACD to topical treatment must be suspected when dermatitis is not controlled with conventional topical treatment.

Each drug applied on tegument may determine sensitizations of different intensities. The location of lesions varies according to the indication and site of application of treatment:

- Extremities, neck, and back are zones affected by NSAIDs.
- Eyelid eczema is typical of eyedrops.
- Auditive external conduct of topical antibiotics.
- Anus and external genitals are affected frequently by ester topical anesthetics.
- Hands appear to be the most frequently affected site in professionals of health and veterinaries or farmers.
- Airborne allergic dermatitis and photoallergic dermatitis affecting exposures areas are typical in occupational dermatitis.

Topical drugs in folds, under occlusive dressings, or in transdermal devices have their logical location in the site of application, but as a result

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of prolonged exposure, the reaction could spread to distant sites (autoeczematization), and even generalization may occur.

Co-sensitization (simultaneous sensitization to not structurally related drugs) to two or more allergens is common in individuals with chronic dermatosis. Also cross-reactivity (simultaneous sensitization between drugs with similar molecular structure) is frequent, for example, topical corticosteroids or anesthetic of the ester group.

When a topically sensitized patient receives the same drug or a chemically related substance by another route (oral, intramuscular or endovenous injections, rectal, vaginal, intra-articular, inhalation or percutaneous), a systemic dermatitis can appear. This entity was described with a large list of drugs (para-amino compounds, antibiotics, antivirals, mercury compounds, etc.). In these cases, clinical picture may appear with different manifestations. The most common is generalized maculopapular rash which may lead to erythroderma even with general symptomatology accompanied.

Common Allergens

The list in medical literature of drugs able to produce ACD is large because topical medicaments are a frequent source of contact, as well they are good sensitizers. It is usually the therapeutic drug itself which acts like a sensitizer, but also other ingredient of topical treatment may be the culprit. Most common include antibiotics, nonsteroidal anti-inflammatories, local anesthetics (LA), antimycotics, corticosteroids, antivirals, antihistamines, and transdermal therapies.

Antibiotics and *antimicrobials* are frequently implicated in contact allergy. Aminoglycosides, especially neomycin, mainly found in ophthalmic and ear preparations, are the most important in this group causing ACD, probably due to a wide use. There is a high grade or cross-reactivity between different aminoglycoside, with the exception of streptomycin. This group of antibiotics has been described like a cause of ACD in veterinaries and health workers (Hjorth and Weissmann 1973; Veien et al. 1980). Bacitracin is another antibiotic which may cause contact allergy, especially in leg ulcer/stasis dermatitis patients, who often react simultaneously with neomycin and polymyxin B. In the past, penicillin and sulfonamides have been the major sensitizers, but nowadays are hardly used topically, and reports of sensitization are rare. *Antimycotics* can cause ACD too. Nowadays, imidazoles are the most commonly used and are not strong sensitizers, but several cases of ACD have been reported. Cross-reaction and systemic contact dermatitis have been described.

Topical antiseptics are very used and may cause ACD:

- Nitrofurazone, used in dressings for wounds and burns, is a well-known sensitizer and can induce severe reactions.
- Thimerosal used in merthiolate tincture and as preservative in vaccines and toxoids and lens solutions may cause ACD. Patients allergic to thimerosal have a risk of photoallergy to piroxicam due to thiosalicylic moiety of the chemical structure.
- Povidone-iodine is the most extensively used local antiseptic. It is very irritant and can cause skin necrosis, but there are a few reports of contact allergy too.
- In children with atopic dermatitis, antiseptic chlorhexidine represents one of the most frequent sensitizers.

Among *local anesthetics* (LA), the most implicated in ACD is the ester derived from para-aminobenzoic acid. Anesthetics in this group are benzocaine, procaine, tetracaine, cocaine, and proxymetacaine. Benzocaine is used to treat anus or vulvar pruritus and hemorrhoids. Cross-reaction with others compounds of the para-amino group, especially with p-phenylenediamine, may occur. Amide LA (lidocaine, bupivacaine, articaine, mepivacaine, prilocaine, procainamide, dibucaine, or cinchocaine) are less potent sensitizers. They do not have cross-reaction between them neither with para-amino group. However, as they are now more used than ester LA, various cases of allergy are being reported.

ACD to topical or injectable *antiviral drugs* is an uncommon observed entity. However, in

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consideration of the widely use of these drugs exists substantial potential to induce contact dermatitis. Almost 15 agents have been identified like contact sensitizers. Tromantadine hydrochloride and acyclovir are the two most widely prescribed. Most skin reactions are mild and transitory, and allergy is probably due to the vehicles of drugs. There are also cases of systemic contact dermatitis and cross-reaction between them (Angelini et al. 1986; Holdiness 2001).

Topical corticosteroids and *modern wound dressings* are other causes of ACD to topical drugs.

Chemical components in topical treatments (*vehicles* like petrolatum or lanoline, emollients, emulsifiers, humectants, *preservatives*, *fragrances*, and components of the adhesive layer in transdermal therapeutic systems) may also induce ACD (Brandão and Goossens 2011). Lanoline and parabens are frequent sensitizers in patients with leg ulcers and stasis dermatitis.

Topical Chinese drugs can induce sensitization especially due to colophony, fragrances, and myrrh (Chen et al. 2003).

In the past, topical antihistamines have been reported like common sensitizers. Ethanolamine group can cause ACD and photoallergic contact dermatitis. Nowadays, topical antihistamines are much less employed, but allergy to oral antihistamines is described.

There is a large list of others topical drugs which may cause ACD: drugs in transdermal therapeutic systems, acaricides, minoxidil, zinc pyrithione, metronidazole, etc. (Brandão and Goossens 2011).

Diagnosis

When ACD is suspected, the study is based on patch testing with an established procedure in standardized protocol. Nevertheless, in the case of ACD to topical drugs, diagnosis is often a challenge for the physician, and frequently distinction between allergic and irritant dermatitis could be difficult. Before any investigation, a detailed assessment is required, taking into account the history of the patient and a clinical examination. Diagnosis will be achieved having in mind multiple variables. Before patch testing, the history identifies potential causes of allergic contact dermatitis and the materials to which individuals are exposed. Knowledge of the different forms of clinical presentation and data about not only contact substances used at the moment of the study but also others used in the past is mandatory. Clinical significance of the findings has to be correctly determined because they can exit both negative and positive false results.

In all the cases, national or international baseline series for patch testing, commercial drug batteries (NSAIDs, corticosteroids, antibiotics, etc.) and in addition suspected or related drugs would be tested. When a photoallergy is suspected, a *photopatch testing* is necessary.

When suspecting contact allergy in the periorbital area, patch testing should be considered in order to identify and avoid offending allergens (Landeck and John 2013). Testing to substances from a standardized ophthalmic tray is recommended, but it is preferable to test the actual drops or creams since many chemicals which are present in ophthalmic drugs are not available as commercial test allergens.

Stasis dermatitis and leg ulcer patients are considered high-risk patients to suffer a contact allergy to several topical treatments, and those circumstances may suppose a difficult diagnosis. Information about all treatments they have received in a long time is necessary.

In some cases, a previous open patch test would be necessary if the suspected drug as a cause of dermatitis could produce strong responses in closed patch testing. Repeat open application test (ROAT) can be used to determine whether a reaction is significant in individuals who develop weak reactions to a chemical in the patch tests.

Bacterial or fungal culture would be necessary to exclude a secondary infection, indicated specifically for dermatitis of the hands and feet.

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Skin biopsy may help to exclude other cutaneous disorders.

Management

When the causative agent or agents have been identified, their removal and avoidance is essential to recover skin damage. Measures to prevent new reactions are mandatory like avoiding other cross-sensitizing drugs.

A list of individual products which are safe or unsafe to use will be hand over to patient. Companies often change their formulations. It is safer to encourage the patient to read the product labels. The ingredient list on product labels will have two headings, covering the active ingredients and the excipients (vehicles, preservatives, and emulsifiers) necessary to make up the preparation.

Emollients and topical corticosteroids could be prescribed taking into account the possibility that allergy to these agents can exist. A variety of symptomatic treatments (antihistamines) can provide short-term relief of pruritus. In serious dermatitis, the use of systemic corticosteroids can be needed.

Other tips regarding the treatment of patients with chronic dermatitis and ACD are:

- When exudates are a problem, a zinc paste can be used to protect the surrounding skin.
- If bandages are causing damage by friction, a layer of cotton tubular gauze under them could be applied.
- Do not use adhesive tapes directly on the skin to secure dressings.
- Avoid the use of antiseptics if possible.
- If it is necessary to clean the wound, use tap water or saline solution.

Cross-References

- ▶ Allergic Contact Dermatitis
- ▶ Atopic Dermatitis
- ▶ Contact Dermatitis Due to Topical Traditional Chinese Medicine
- ▶ Contact Dermatitis in Children
- ▶ Contact Sensitization to Modern Wound Dressing
- ▶ Cutaneous Drug Reactions
- ▶ Delayed Allergic Hypersensitivity to Corticosteroids
- ▶ Fragrance Contact Allergy
- ▶ Oral Antihistamines
- ▶ Oral Corticosteroids
- ▶ Photopatch Test Baseline Series
- ▶ Preservatives Contact Allergy

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Contact Dermatitis Due to Topical Traditional Chinese Medicine

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Synonyms

Complementary and alternative medicine; Traditional Chinese medicine; Traditional herbal Chinese medicine; Traditional topical Chinese medicine

Definition

Allergic contact dermatitis caused by certain topical drugs or substances present in the traditional Chinese medicine pharmacopoeia.

Introduction

Complementary and alternative medicines (CAM) enclose several categories – including traditional Chinese medicine (TCM) – which exist outside the extent of traditional medical therapeutics in which their efficacy and safety are yet to be determined (Mainardi et al. 2009).

Historical Background

Chinese herbal medicine originated in China rooted in the ancient philosophy of Taoism. TCM is considered as a medical system itself which has evolved empirically over 5,000 years to its present development and systemization of knowledge. Nowadays, TCM is closely practiced along with Western medicine in many of China's hospitals and clinics.

Epidemiology

The use of CAM in the United States has been increasing at a substantial rate over the past two decades from a total of 34 % (427 million) to 42 % (628 million) of therapies (Eisenberg et al. 1998). Topical traditional Chinese medicines (TTCM) are largely sold as OTC products both in the East and in the Asian communities from some European countries and the United States (Heimall and Bielory 2004). In Singapore, the use of TTCM is common as self-prescribed or Chinese physician-prescribed remedies. In a cross-sectional analysis of a cohort of community-living adults aged above the age of 65 years in this country, the prevalence of TCM use was 25.3 %, among whom 52 % reported concurrent use of Western prescription medicines (Ng et al. 2004). Although TCM is usually considered very safe, severe side effects of systemic TCM such as hypersensitivity, idiosyncratic reactions, hepatotoxicity, or renal failure have been described (Huang and Tao 1989). Allergic contact dermatitis (ACD) from TCM is rarely reported; however, the incidence of such report is increasing (Leow et al. 1995; Leow 1997). The incidence of topical reactions to drugs varies from one area to another and from one country to another, depending on local prescribing and self-medication habits. The real prevalence of ACD from TTCM has not been yet determined.

Allergens

Most TCM drugs come into the market in a processed form (herbal drugs are steamed, boiled, or treated with solutions or minerals) to destroy or eliminate toxic compounds or to stabilize some drugs or their constituents. In addition, the quality of TCM drugs very often does not meet the standards of international regulatory authorities. Not all identity proofs of TCM methods found in the existing Chinese pharmacopoeias are compatible with those in other national pharmacopoeias and must be improved or altered.

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Another conflicting issue arises in the quality control because of the nonuniform Chinese nomenclature for the same plant in the different regions of China. This uncertainty may be related to adulterations, substitutions, or falsifications in TMC drugs (Yang 2010).

A patch test study from Taiwan investigated in 2003 the incidence of ACD to the components of TCM in 30 patients with diagnosed ACD from TCM. The herbs associated with the most frequent positive reactions were *Flos Caryophylli*, *Radix Angelicae Pubescentis*, *Cortex Cinnamomi*, *Cortex Radix*, *Acanthopanacis*, *Caulis Impatientis*, *Resina Draconis/Sanguis Draconis*, *Fructus Cnidii*, *Radix Gentianae Macrophyllae*, and *Rhizoma Ligustici Chuanxiong* (Chen et al. 2003).

As previously described in several reports, concomitant allergy to colophony was also found in most of these positive reactions (Li and Wang 2002). Terpenes (camphor and menthol) and essential oil extracts (eucalyptus and cinnamon) have been described as the main ingredients contained in Chinese herbal plant extracts (Lim and Thirumoorthy 2005).

Clinical Manifestations

The dermatologic adverse effects of topical and oral herbal treatments are numerous, ranging from allergic contact dermatitis reactions to pruritic eruptions, urticaria, angioedema, and Stevens-Johnson syndrome.

The most common dermatologic adverse reaction from TTCM is ACD (Priya Sen et al. 2010). ACD from TTCM has been firstly reported in 1990 (Lee and Lam 1990). Myrrh has also been reported by the same authors to be the causative allergen in dermatitis due to bonesetter's herbs (Lee and Lam 1993). Subsequent reports from China have also shown ACD from TCM to be associated with a high rate of patch test positivity to fragrance and colophony (Li and Jing 1995; Koh et al. 1997; Machet et al. 2004). Li and coworkers patch tested in 2002 some of the suspected herbs in TCM (mast, myrrh, safflower, and cassia) showing that 12 out of 20 patients (60 %) reacted to at least one of the four allergens. The same study found a high positivity rate (91 %) to either fragrance mix, colophony, or both on patch testing, supporting the hypothesis that these substances are the main contact allergens in TCM (Li and Wang 2002).

Lim et al. described the sensitizing potential of TTCM as almost all 44 patients with chronic leg venous ulcers (94.1 %) who had a history of TTCM usage had at least one positive patch test reading (Lim et al. 2007).

It has been proposed that patients who are allergic to fragrance mix, Myroxolon Pereirae resin, or colophony should avoid topical TCM (Chen et al. 2003). In addition, it should be considered that the frequent practice of applying TCM with occlusive tapes on edematous, erythematous, or even abraded skin increases the chance of contact sensitivity to the applied substances.

False-positive irritant reactions need to be considered in the interpretation of any patch test reading. Irritant contact dermatitis to TTCM has been associated with the use of Zheng Gu Shui and White Flower Oil (Leow 1997).

Interestingly, although the presence of heavy metals in TTCM has been suspected, the frequency of concurrent allergies to metals (nickel sulfate, cobalt chloride, potassium dichromate, and ammoniated mercury) was not significantly increased in a Taiwanese study series (Chen et al. 2003).

Conclusions

Topical traditional Chinese medicaments are largely sold as OTC products, not only in the East but also in Asian communities from different countries.

Active components include terpenes, salicylates, and essential oil extracts that may induce both skin sensitization and irritation. Colophony, fragrances, and myrrh are common allergens in these preparations.

Preventive interventions in TTCM such as replacing some of the plant extracts to those

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components with lower allergenicity, reducing their concentration, and correct labeling of the dosage of each component and accurate chemical compounds may improve the safety of TTCM.

Cross-References

- Allergic Contact Dermatitis
- Contact Dermatitis Due to Plants
- Contact Dermatitis Due to Topical Drugs
- Cutaneous Drug Reactions
- Diagnostic Terms: Atopy
- Fragrance Contact Allergy
- Herbal Remedies
- Homeopathy in the Treatment of Allergic Diseases
- Plants, Allergic Contact Dermatitis from

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Contact Dermatitis in Children

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Synonyms

Contact eczema in children

Definition

Allergic contact dermatitis (eczema) is a cutaneous delayed reaction that occurs in pediatric population.

Epidemiology

It has been thought during the past that contact dermatitis was a disease exclusively for adults

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and with very little impact on the child population (Wöhrl et al. 2003). This idea that its prevalence in children was low has been rebutted with the epidemiological studies published in recent years (Morren and Goossens 2011). However, the great variability and the different existing methodology between different studies make them hardly comparable between them and that actual incidence and prevalence are still unknown (Wöhrl et al. 2003). In an unselected population (Mailhol et al. 2009), for instance, one consisting of schoolchildren, the prevalence is about 20 %, while in a selected population, i.e., children suspected of contact allergy or suffering from atopic or other types of dermatitis, the prevalence is found to be variable, for example, related to geographical origin, with a mean of 40 % (Morren and Goossens 2011).

Natural History

Sensitization can start in the first year of life, but the prevalence increases with age as well as with successive exposition. One of the main problems in children as the most common is dermatitis (De la Cuadra et al. 1990) such as the atopic dermatitis (Oranje et al. 1994) and irritant contact dermatitis (ICD). The last one (ICD) is very variable and many times it is practically impossible to differentiate it from contact dermatitis: papular eruption, flaking, or erythema, usually simply limited to the place of contact and without overflowing.

They may be acute, caused by very aggressive agents usually accidental, or chronic. It is not known if allergic contact dermatitis is more or less frequently associated with atopy. The possibility of allergic contact dermatitis in atopic children has to be considered, particularly if the distribution of the lesions is asymmetrical. When the dermatitis is located around the umbilicus, it can be induced by nickel. Also when an airborne pattern is found, we can think of pollens such as *Compositae* or even in mites. If dermatitis persists after treatment, you can think in compound of the treatment such as disperse dyes, topical medication (Gracia Bara et al. 1999; Morren and Dooms-Goossens 1994), or emollients (Martorell et al. 2011).

Differential Diagnosis

Diaper dermatitis with multifactorial etiology is caused by prolonged contact with wet and dirty diapers. Stool acidity, moisture, occlusion, and friction have been postulated as possible triggers. This has been associated with the production of ammonia by some bacteria with urease activity which breaks down the urea in urine. The lesions are located on the areas of application, with a honeycomb appearance with respect to the inguinal folds. The contact allergy to any of its components is outstanding.

Juvenile Plantar dermatosis, with unknown etiology, is related to the friction and occlusion of footwear favored by hyperhidrosis. This condition is characterized by erythematous, dry, flaky skin, and looking bright, affecting the anterior third of both feet and above all to the ball of the first finger.

Perioral dermatitis caused by moisture and maceration present in this region by constant contact with saliva, food, and pacifier, as well as frictional dermatitis that some children develop when walking and crawling over rough surfaces resulting to lichenification of the skin of the elbows, knees, and backs of the hands.

Allergens

Substances capable of producing contact dermatitis as well as all those capable of producing an allergic reaction are called allergens.

The following is a list of the allergens most frequently involved in contact dermatitis in European children (Seidenari et al. 2005):

1. **Nickel**: Main sources are contact with jewels (in girls), frames for sunglasses, and belt buckles.
2. **Mercury**: Mainly, contact with antiseptics (mercurochrome) and thermometer breaks.
3. **Balsam of Peru**: Mainly in adolescents by contact with cosmetics.

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4. **Gums**: Although there are countless sources of contact, the more important is perhaps the use of athletic shoes.
5. **Cosmetics:** Products specially formulated for children such as formaldehyde and its releasers, parabens, methyl(chloro) isothiazolinone, Euxyl K400®, and the antioxidant butylhydroxyanisole (BHA). Recent studies have confirmed that cosmetics could be the most frequent cause of contact allergy in children.
6. **Potassium dichromate**: Usually after contact with dyed skins (shoes, coats, chrome-plated objects, etc.).
7. **Cobalt**: As content in paints and pencils, wax, metal objects, etc.
8. **Wood tar**: Mainly used in creams and ointments to treat children with eczema or psoriasis.
9. **Benzocaine**: Used in children as a topical anesthetic and also to relieve the itch.
10. **Neomycin**: Used as an antibacterial agent in many creams and ointments used in children to treat cuts, burns, and even skin infections.
11. **Tattoos, toys, shoes, and electronic devices**: Finally, in some cases, the occupational allergens might also produce contact dermatitis (Johnke et al. 2004).

Diagnosis

Diagnosis of contact dermatitis is based on the realization of a good clinical history complemented with proofs known as patch (Vigan 2008). Testing patch (also called patch tests) is used for more than 70 years. Patches with culprit substances are applied at the upper back for 48 h, watching for the skin's response (Jacob et al. 2008). In order to obtain reliable results, it is very important (Beattie et al. 2007) that these substances are maintained at least 48 h in contact with the skin. Once it has been removed, first reading of the result is done at 48 h and the second at 72–96 h, although it can sometimes be even later according to the suspicious substances (Storrs 2008). These patch tests are not affected by antihistamine intake.

However, even though the lack of chemical exposure of children compared to that of adults and the small patch test area and, especially with younger children, the risk of active sensitization, it has been proposed testing with an abbreviated standard patch test series of less than the conventional 33 allergens in adults (Vigan et al. 1994).

Proposed Recommended Battery for Diagnosis in Children

The Group of Research Studies in Dermato-Allergy of France (*Groupe d'Etudes et de Recherche en Dermato-Allergologie – GERDA, France*) created a group of Vigilance in Dermato-Allergology which proposed in 1990s to restrict the baseline series to 16 allergens (Vigan et al. 1998). This proposal was based on four studies and a large multicenter study in 11 different centers performed in near to 1,000 children below the age of 15, tested for 2 years.

The 16 allergens suggested finally were potassium dichromate, neomycin, thiuram mix, PPD-base, cobalt chloride, formaldehyde, colophonium, balsam of Peru (*Myroxylon pereirae*), wool wax alcohols (lanolin alcohol), mercapto mix, paraben mix, PTBP-FR, fragrance mix, nickel sulfate, methyl(chloro)isothiazolinone, and mercaptobenzothiazole.

More recently, based on a subsequent study conducted in Germany, an expert panel of the German Contact Dermatitis Research Group recommended in 2007 that 12 allergens should be tested in children (Worm et al. 2007). The 12 allergens were:

- Nickel sulfate 5 % pet
- Thiuram mix 1 % pet
- Colophony (colophonium) 20 % pet
- Mercaptobenzothiazole 2 % pet
- Fragrance mix I 8 % pet
- Fragrance mix II 14 % pet
- Mercapto mix 1 % pet
- Bufexamac 5 % pet
- Methyldibromo glutaronitrile 1 % pet
- Methyl(chloro)isothiazolinone 100 ppm aq (water)

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- Neomycin 20 % pet
- *Compositae* mix 6 % pet

And this panel also recommended five additional allergens but only tested if the history suggests contact allergy. These 5 additional allergens were:

- p-tert-Butylphenol formaldehyde resin 1 % pet
- Potassium dichromate 0.5 % pet
- Wool alcohols (lanolin alcohol) 30 % pet
- Disperse blue mix 1 % pet
- Paraphenylenediamine 0.5 pet

Conclusion

- The history and localization of the dermatitis are crucial for the diagnosis of allergic contact dermatitis.
- Patch testing in children is safe, and the same patch test concentrations as in adults can be used although, in case of any doubt, lower patch test concentrations should be tested.
- Testing with an abbreviated standard series is recommended.
- The most important allergens observed in this population are metals such as nickel.

Cross-References

- ▶ Allergic Contact Dermatitis
- ▶ Nickel Allergic Contact Dermatitis
- ▶ Nickel Contact Dermatitis
- ▶ Oral Antihistamines

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Contact Sensitization to Modern Wound Dressing

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Synonyms

Contact dermatitis to bandages; Sensitization to modern wound dressing (WD)

Definition

Wound dressings are local therapeutic agents intended to create an optimal environment for wound healing, with specific properties according to the type and physiologic healing stage of the wounds (Goossens and Cleenewerck 2010). Allergic contact dermatitis (ACD) to modern wound dressing is a delayed-type hypersensitivity reaction caused by any component of these medical products.

Introduction

In the past few decades, wound dressings (WDs) have shifted from simple dry wound coverings to dynamic multicomponent-layered dressings that can promote wound hydration, healing, hemostasis, and immobilization and prevent infection and hematoma/seroma formation (Butler and Mowad 2013).

Important advantages of new dressings are the atraumatic character, effective curative action, and reduced therapy time (Butler and Mowad 2013).

Some dressings incorporate biologically active component as anti-inflammatory or analgesic drugs, antibiotic, antifungal, antiseptic, growth factors, and proteolytic enzymes (Yudanova and Reshetov 2006).

Classification of Wound Dressing

Most common modern WD (Armstrong and Meyer 2013) are:

- **Hydrogels** are a matrix of various types of synthetic polymers with 95 % water formed into sheets, gels, or foams that are usually sandwiched between two sheets of removal film.
- **Hydrofiber dressings** are composed entirely from sodium carboxymethyl cellulose (CMC) which is a water-soluble, anionic derivative of cellulose. These fibers are used to make soft, nonwoven dressings which have the ability to gel upon contact with fluid.
- **Hydrocolloids dressings** are composed from an elastomeric (polyurethane foam/film) adhesive and gelling ingredient. Common gelling agents are CMC, pectin, and gelatin.
- **Alginate dressings** are linear polysaccharides found abundantly in nature as they are the major component of marine brown algae. Some alginate dressings contain silver/zinc inclusions to improve antibacterial activity and blood clotting ability, respectively.
- **Foam dressings** are made from the synthetic polymers, polyurethane, and silicone. Some foam dressings can have an adhesive dressing, an extra layer at the wound surface to prevent adherence, or an occlusive polymeric backing layer to prevent excess fluid loss and bacterial contamination. Foam dressings can be treated with antibacterial agents such as polyhexamethylene biguanide (PHMB) and silver.

Prevalence

The allergenic potential of modern WD should not be underestimated. There was a significant correlation between number of sensitizations to WD and wound duration (Renner et al. 2013; Barbaud et al. 2009).

Contact allergy is favored by different factors (Goossens and Cleenewerck 2010):

– Use, over a long period of time, of molecules that have strongly sensitizing properties

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- Alteration of the skin barrier, favoring the skin penetration of potentially allergenic substances (Tavadía et al. 2003)
- Occlusion, which also increases skin penetration
- Hemodynamic troubles: local hypervascularization with the afflux of lymphocytes (which play a role in delayed-type hypersensitivity)
- Increase in the number of Langerhans cells, in and around the ulcer

Most affected groups are patients with chronic venous insufficiency (CVI) (Cravo et al. 2008) and cutaneous surgery, burn patients, and those with elastic leg support bandages (Lehnen et al. 2006).

The prevalence of ACD is not well known due to several factors: very few reports in the literature and with short series of patients, lack of homogeneity between the series, and, in most cases, the complete composition of WD is not declared.

Sensitizations to hydrogels seem to be most common with 9–23 % of the tested patients reported to be patch test positive. Sensitization to hydrocolloids has been reported in approximately 11–52 % of patients (Renner et al. 2011).

Allergens

A large list of allergens are found causing allergic contact dermatitis (ACD), some of them headed by ointment bases, others are active principles or topical drugs.

Common allergens in **adhesives** include colophony, benzoyl peroxide, rubber accelerators, antioxidants, and acrylates. Of these allergens, colophony (rosin) is the most frequent cause of ACD from adhesives. Abietic acid and Abitol are the main sensitizing components.

ACD to **hydrocolloids** can be caused by sensitization to Pentalyn (pentaerythritol ester of hydrogenated rosin) (Timmer-de Mik and Toonstra 2008) or to other ester gum rosins, for example, glyceryl rosinate, or to polyisobutylene derivatives. These substances act like tackifying agents (Rietschel and Fowler 2008).

Patients with positive reactions to hydrocolloid dressings might show cross-reactions also to unmodified colophony, but often they do not because the described allergens are processed and modified (Renner et al. 2013).

Regarding **polyurethane foam**s, sensitization may arise because of the butyl methacrylate/methyl methacrylate containing adhesive borders (Renner et al. 2013).

Propylene glycol, a common preservative, is responsible of sensitization in **hydrogels** (Gallenkemper et al. 1998).

Compounded tincture of benzoin (CTB) and Mastisol are frequently applied to the skin to increase the adherence of surgical tape or other adhesive bandages. Several reports of ACD to tincture of benzoin and Mastisol have been reported in the literature (Butler and Mowad 2013; Sasseville et al. 2009; Worsnop et al. 2007).

Topical drugs used with occlusive dressings and fixatives are often applied to inflamed or injured skin in the postsurgical setting, which can increase the chances of ACD:

- **Antibiotics:** ACD associated with topical antimicrobial agents is an increasing problem in the postoperative wound care period. Neomycin was the most common cause of ACD. Bacitracin was also a common culprit. There is a risk of co-reactivity between these two agents.

Polymyxin B and mupirocin were not significant allergens (Sheth and Weitzul 2008). For closed wounds, the use of topical neomycin postoperatively should be avoided (Mallon and Powell 1994).

- **Topical Steroids:** Contact dermatitis to topical corticosteroids has been widely recognized for the past 20 years with prevalence between 0.55 % and 5.98 %. Currently, the most common allergen to cause a positive patch test result is tixocortol-21-pivalate with a prevalence of 2 %, followed by triamcinolone acetonide (0.8 %), hydrcortisone-17-butyrate (0.7 %), and clobetasol-17-propionate (0.3 %), with desoximetasone producing the lowest likelihood of ACD at a prevalence of 0.2 %.

Systemic toxicity appears to be exceptional, but propolis is a potent contact sensitizer, and the

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use of propolis products not infrequently leads to sensitization and allergic contact dermatitis.

Others possible allergens are:

- **Vehicles** (e.g., lanolin)
- **Preservatives** (e.g., quaternium-15, isothiazolinones, parabens)
- **Stabilizers** (e.g., ethylenediamine)
- **Silicone**
- **Suture material:** If suture ACD is suspected, it has been suggested to consider testing with suture sewn through the skin, as opposed to placing over the skin, as a method of discerning the etiology of suture line ACD (Butler and Mowad 2013).
- **Dermabond (2-octyl cyanoacrylate):** If allergy to Dermabond, or any other allergen not on the standard series, is suspected, a stand-alone epicutaneous test can be helpful (Butler and Mowad 2013).
- **Adaptic gauze**: Sensitization was observed in very few reports (de Waard-van der Spek et al. 2007). In these cases sensitization to sorbitan sesquioleate may be the causative agent (Renner et al. 2013).

Diagnosis

Most relevant allergens are included into the European baseline patch test series (Motolese et al. 2009).

Patch testing with WD "as is" and patch tests of ingredients of topical preparations: metals, fragrances, preservatives, adhesives, or methacrylates should be performed (Renner et al. 2013).

Patients where ACD from hydrocolloid dressings is strongly suspected and colophony tests are negative, patch testing to modified colophony derivatives (glyceryl rosinate) should therefore be performed (Butler and Mowad 2013; Pereira et al. 2007).

Cross-References

- ▶ Allergic Contact Dermatitis
- ▶ Contact Dermatitis Due to Topical Drugs
- ▶ Delayed Allergic Hypersensitivity to Corticosteroids

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Contact Urticaria and Protein Contact Dermatitis (to Asparagus, Cow's Hair, Seafood, Etc.)

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Synonyms

Contact dermatitis; Urticaria

Definition

Proteins that penetrate through the skin can elicit two forms of allergic reactions. If they are bound by IgE antibodies on mast cells, a localized immediate-type allergic reaction can occur. Sensitized people typically develop pruritic hives about 20–30 min after skin contact with the allergen. In case of additional systemic symptoms like asthma or anaphylaxis, one speaks of contact urticaria syndrome. In addition, proteins can also induce a cutaneous delayed-type hypersensitivity reaction after skin contact, called protein contact dermatitis. This occurs either in conjunction with contact urticaria, after the urticarial reaction has subsided, or independently of it. The protein allergens are different kinds of food (like vegetables, meat, fish, seafood), animal dander, or natural rubber latex.

Cross-References

► Food Allergy, Overview
► Urticaria

Cotinine

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Synonyms

(5*S*)-1-Methyl-5-(3-pyridyl)pyrrolidin-2-one

Definition

An alkaloid found in tobacco that is a metabolite of nicotine and used as a marker in serum, urine, semen, and hair of tobacco smoke exposure.

Introduction

Tobacco smoke contains approximately 4,000 toxic chemicals (Hwang et al. 2012). Currently, more than 1.3 billion people smoke or use tobacco, and nearly 5 million worldwide die of diseases associated with tobacco smoke exposure every year. Environmental tobacco smoke (ETS) is defined as tobacco smoke produced by an active smoker both from the exhalation of smoked tobacco and by burning the end of a cigarette or cigar which is then inhaled by a nonsmoker. ETS consists of particles which range in size from 2.5 to >250 nm. Particles in the 75 to 250 nM range are effectively accumulated in the airway.

Biomarker of Tobacco Smoke Exposure

Cotinine is the major degradation product of nicotine metabolism. Approximately 80 % of nicotine is converted to cotinine in the C-oxidation

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pathway (Tricker 2003). Cotinine (formula: $C_{10}H_{12}N_2O$) is an alkaloid with a molecular mass of about 176 g/mole. Its biological mechanism of action is analogous to nicotine in that it binds to, activates, and desensitizes the nicotinic acetylcholine receptor. Because of its relatively long biological half-life in serum, cotinine provides a useful estimate of passive (secondary or secondhand) tobacco smoke exposure. This marker is especially important for children who are being evaluated for asthma and other pulmonary conditions.

Passive smoke exposure is a risk factor for the development and exacerbation of asthma. An estimation of the risk associated with secondhand tobacco smoke exposure depends on an accurate analytical measurement of nicotine or its major metabolite, cotinine. Cotinine in particular has been widely used as a biomarker for the assessment of passive smoking exposure using plasma, urine, saliva, semen, and hair. This is because cotinine's biological half-life in serum is 16–20 h, while nicotine concentrations reduce by half in 2 h (Jarvis et al. 1988). This permits assessment of passive smoke exposure from a previous 2- to 3-day period. More recently, hair analysis has been used as a less invasive method for detecting the presence of nicotine exposure. Because nicotine and its metabolite cotinine accumulate in hair during hair growth, it is a unique measure of long-term cumulative exposure to tobacco smoke.

Quantitative Analysis of Cotinine in Biological Fluids

Quantitative levels are measured in various biological fluids including serum/plasma, urine, semen, and hair using colorimetry, chromatography, and immunoassay. Immunoassay which displays an analytical sensitivity for cotinine of 1 ng/ml is the most widely used analytical method. Liquid chromatography/tandem mass spectrometry, however, can detect nicotine and cotinine in as little as 1 mg of hair (Ryu et al. 2006).

In one study (Vine et al. 1993), cotinine concentrations were measured by immunoassay in blood, urine, and semen of 88 subjects (40 nonsmokers, 23 light smokers, and 25 heavy smokers). Participants were healthy white men aged 18 to 35 who provided semen, urine, and blood specimens and completed a self-administered questionnaire which examined their smoking habits and demographic characteristics. Results of the cotinine analysis showed that among the 48 smokers, elevated cotinine levels were found in 100 % of urine and semen specimens and in 98 % of blood specimens. However, cotinine levels were highest in the urine. Levels of cotinine in the serum or urine were shown to reflect the number of cigarettes smoked or the longevity of passive smoke exposure. For instance, serum cotinine levels <10 ng/ml are considered an indicator of an individual who is not actively smoking and who has had negligible passive smoke exposure. Cotinine levels from 10 to 100 ng/ml are associated with light smoking or moderate passive exposure. Serum levels above 300 ng/ml are detected in heavy smokers. The 95 % confidence interval of levels of cotinine in serum of an individual who smokes 1–19 cigarettes a day is from 62 to 282 ng/ml. This median level of cotinine increases to 322–902 for an individual who smokes 20+ cigarettes a day. Median level of cotinine in urine for nonsmokers is 17 ng/ml (95 % confidence interval between 13.8 and 21.9 ng/ml) (Vine et al. 1993). When cotinine levels in a spot urine specimen reach 30 ng/ml, this is considered an indicator that the individual has been passively exposed to tobacco smoke or they have been lightly smoking. Urine levels 500 ng/ml or more are detected in active smokers. For smokers of 1–19 cigarettes a day, the 95 % confidence interval is 39–4,308 ng/ml.

Analogous results were observed by Wall et al. (1988) who examined 98 subjects between the ages of 24 and 66 years. They measured cotinine by gas chromatography in serum urine and saliva from all study subjects. Mean levels of cotinine in saliva and serum were comparable (e.g., 78 ng/ml serum; 67 ng/ml saliva for active smokers of <10 cigarettes per day). Urine levels for the same group were higher (mean: 647 ng/ml), but they were more highly variable among intersubject specimens. This variability improved following correction using urine creatinine.

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Some investigators consider hair nicotine to be a more precise biomarker of exposure to environmental tobacco smoke than urine cotinine. The level of hair cotinine in unexposed nonsmokers was 0.3–0.4 ng/g in children. A level of 0.2 ng of cotinine per mg of hair is thus considered an accurate cutoff value between exposed and nonexposed children (Florescu et al. 2007).

Other studies have compared urine cotinine and hair nicotine as biomarkers of exposure to environmental tobacco smoke (ETS) (Al-Delaimy et al. 2002; Al-Delaimy 2002). Hair nicotine was shown to be the most precise and accurate measure of ETS in comparison to urinary cotinine levels. Cotinine was also present in hair but at levels 10 times lower than nicotine.

Cross-References

- ▶ Asthma Variants: Allergic Asthma
- ▶ Asthma Variants: Cough-Variant Asthma
- ▶ Diseases in DDx of Asthma: COPD
- ▶ Diseases in DDx of Asthma: Differential Diagnosis of Asthma

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Cow's Milk Allergy

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Synonyms

IgE-mediated cow's milk allergy; Milk allergy

Definition

Cow's milk allergy is an adverse immune response to dietary antigen in cow's milk.

Introduction

Cow's milk allergy is the most common food allergy in young children but is rare in adults (Rona et al. 2007). The term "cow's milk allergy" is often used to describe food hypersensitivity reactions including immunoglobulin E (IgE)-mediated reactions, mixed IgE- and non-IgE-mediated disorders (such as allergic eosinophilic gastrointestinal disorders), as well as non-IgE-mediated reactions (including allergic proctocolitis and food protein-induced enterocolitis syndrome). Additionally, lactose intolerance is at times referred to as cow's milk allergy; however, this is a nonimmune mediated food intolerance and does not represent a true allergy. This entry will focus solely on IgE-mediated cow's milk allergy.

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Epidemiology

Approximately 2.5 % of newborn infants experience a hypersensitivity-type reaction to cow's milk in the first year of life with IgE-mediated reactions accounting for approximately 60 % of these reactions (Sampson 2003). It was previously reported that prognosis for cow's milk allergy was good, with most infants with cow's milk allergy outgrowing their sensitivity by age 3 and approximately 10–25 % of infants retaining their sensitivity up to the second decade (Host et al. 2002). Recently, however, a study found only 19 % of children outgrow their cow's milk allergy by age 4, with approximately 10–20 % of patients over the age 16 with persistent cow's milk allergy (Skripak 2007).

Approximately 35 % of infants with cow's milk allergy will develop allergic reactions to additional foods (Host et al. 2002). Additionally, these infants are more likely to have atopic dermatitis, allergic rhinitis, and asthma (Boyce et al. 2010).

Clinical Features

Cow's milk allergy symptoms often appear during the first few months of life, often within days of starting a cow's milk-based formula. Symptoms can be seen as well, if a breastfeeding mother ingests cow's milk. As seen with other IgE-mediated food allergy, reactions to cow's milk are immediate, occurring within minutes to 2 h after consumption. Symptoms are consistent with that seen in other reactions due to food allergies and can include cutaneous (urticaria, flushing), upper respiratory (nasal congestion, sneezing, rhinorrhea, laryngeal edema, hoarseness), lower respiratory (cough, wheezing), gastrointestinal (nausea, vomiting, diarrhea), and cardiovascular (tachycardia, hypotension, shock) systems (Boyce et al. 2010). Reactions can vary from mild to severe and can cause life-threatening anaphylaxis. In a report of fatal food-induced anaphylaxis in the United States over a 5-year period, 4 out of 31 cases were due to milk ingestion in a milk allergic patient (Bock et al. 2007). These reactions highlight the need for early recognition of signs of anaphylaxis and prompt treatment.

Diagnosis

Cow's milk allergy should be suspected when a reaction occurs in the time frame immediately following ingestion of a food containing cow's milk protein. Close attention should be made to looking carefully at labels of the food ingested. Many foods contain cow's milk proteins including casein and whey as well as lactose sugar among others. A detailed discussion with the patient and family should elicit the following pieces of information: the type of food consumed and quantity, the exact symptoms experienced, the time to onset of symptoms, and the treatment required to resolve the symptoms.

Based on this history, a provider will often proceed with skin prick testing with a small quantity of prepared milk protein extract and/or obtain a small blood sample for evaluation for IgE antibodies to milk protein. Skin prick testing should only be performed by a provider familiar with the procedure of skin prick testing and the interpretation of results.

Specific IgE to cow's milk and skin prick testing can be used together with the history to assess the likelihood of an IgE-mediated cow's milk allergy. Decision points have been published for a specific type of IgE detection technology, CAP system FEIA, proposing diagnostic levels which could predict clinical reactivity with greater than 95 % certainty (Sampson 2001). Again, these levels need to be interpreted by a provider familiar with the technology and appropriate interpretation of the results.

The gold standard for diagnosis is a double-blinded placebo-controlled oral food challenge. However, often the diagnosis is made based on history and skin prick testing combined with specific IgE levels alone. If a challenge is performed, it is often an open food challenge (not blinded) and tends to be reserved for cases where the diagnostic testing and history are not completely clear.

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Management

Management of cow's milk allergy involves strict avoidance of cow's milk proteins. Education should be given to the patient and his or her family regarding how to read a food label for the presence of milk. Mandatory food allergen labeling has been enacted in the United States, requiring food packages to indicate the presence of milk. Some products, however, indicate "may contain milk"; these products should be avoided as well because the risk of reactions to these products is unknown.

For infants and toddlers with cow's milk allergy, elimination of milk from the diet can pose nutritional risks (Fiocchi et al. 2010). As cow's milk is an essential source of fat and protein, it is important that an appropriate substitute be used. Breastfeeding mothers should eliminate cow's milk protein from their diets completely, if they wish to continue breastfeeding. For formula-fed infants, an extensively hydrolyzed formula or amino acid-based formula can be used as a substitute (Fiocchi et al. 2010). If the infant is already tolerating a soy formula, this can be continued. For children over the age of 1, a commercially prepared hypoallergenic formula may be continued. Alternatively, enriched soy formula can be used for patients without soy allergy (Fiocchi et al. 2010).

Families should also be educated regarding the risk of cross-contamination, in which a small amount of cow's milk protein may come into contact with "safe" foods, usually during preparation of foods. This is especially important when dining in restaurants and locations outside of the home.

Education should be given regarding recognition and management of anaphylaxis in case of accidental ingestions. Most providers prescribe injectable epinephrine for all patients with food allergy. A written action plan should be given to the patient's family, describing the exact treatment needed for each type of reaction experienced, and this plan should be discussed. Additionally, the parent and patient should be familiar with how to administer the injectable epinephrine. It is particularly helpful to use a trainer device so that the family member and/or patient can practice using the device.

Children with milk allergy should be monitored for resolution of allergy by follow-up history detailing any accidental ingestions and the reactions provoked, along with repeated skin prick testing and milk-specific IgE levels. Prognostic indicators have been described for developing tolerance to milk in patients with IgE-mediated cow's milk allergy including lower initial level of milk-specific IgE (Skripak 2007), a faster decline in the milk-specific IgE over time (Shek et al. 2004), as well as absence of allergic rhinitis or asthma (Skripak 2007; Levy et al. 2007). If testing results are deemed favorable for an oral challenge, this may be performed in the clinic to document tolerance. If the challenge does not elicit symptoms, milk protein can be reintroduced into the diet.

Conclusions

While cow's milk allergy represents the most common food allergy in children, it is also commonly outgrown. A detailed history is important in making the diagnosis, as are testing modalities including skin prick testing, specific IgE levels, and oral food challenge. Management includes strict avoidance with prompt and appropriate treatment of accidental ingestions.

Cross-References

- ▶ Allergic Proctocolitis and Food Protein-Induced Enterocolitis Syndrome (FPIES)
- ▶ Diagnostic Food Challenges
- ▶ Eosinophilic Gastrointestinal Disorders
- ▶ Epidemiology of Food Allergy
- ▶ Fatal Allergic Reactions to Foods
- ▶ Food Allergens
- ▶ Food Allergy and its Future Treatment
- ▶ Food Allergy, Overview
- ▶ IgE Testing
- ▶ Nutrition in Food Allergy

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Cutaneous Drug Reactions

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Synonyms

Drug-induced skin reactions

Definition

Cutaneous drug reactions are unintended, drug-induced harmful skin responses, which can be confined to the skin or part of a systemic disease and range from mild to severe, life-threatening reactions (Ardern-Jones and Friedmann 2011).

Introduction

With an incidence of up to 15 % in hospitalized patients and about 10 % in outpatient treatments, adverse drug reactions are a common problem in medicine. Early descriptions date back to von Galen (129–199 AD), who reported adverse reactions to a powder. The most common cutaneous drug reactions are rashes (exanthema) with about 40 % and urticaria including angioedema (25 %). Some reactions to drugs, although they are rare, implicate a significant mortality. Those form the subgroup of severe cutaneous drug reactions including erythema multiforme, Stevens-Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN).

Etiopathogenesis

Drug reactions can be divided into two major subtypes. Type A ("augmented") are predictable, dose-dependent toxic reactions like dried skin (xerosis cutis) to retinoids or tiredness to antihistamines. Type B ("bizarre") are unpredictable reactions either immune mediated or caused by other mechanisms. The former include allergic reactions like IgE-mediated urticaria and anaphylaxis, allergic vasculitis due to immune complex formation, or T-cell-mediated drug rashes, the latter intolerance reactions like urticaria and angioedema induced by cyclooxygenase I inhibitors or unclassified drug reactions.

Most immunologic reactions are the result of a specific sensitization against the drug as an allergen. Since many drugs are molecules, which are too small to function as a full antigen, they have to be bound as a hapten to an endogenous protein serving as a carrier (Demoly et al. 2007). Some drugs first need to be metabolized to become a hapten. The allergic reactions can be divided into hypersensitivities type I–IV according to the Coombs and Gell classification with type IV reactions further subdivided by Pichler (Pichler 2003) (Fig. 1). For some drug reactions, for which the etiopathogenesis is still unknown, a direct activation of the immune system without prior sensitization is discussed.

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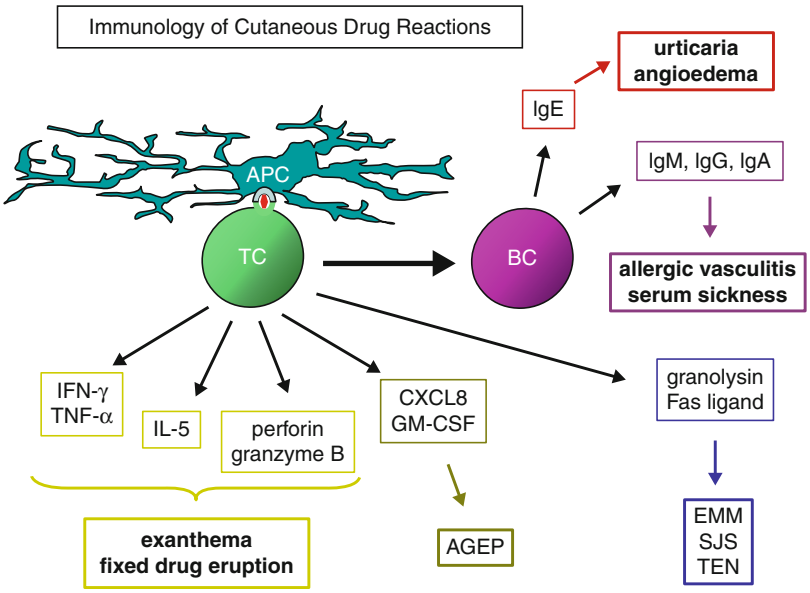

Cutaneous Drug Reactions, Fig. 1 Diagram provides an immunologic mechanism for various types of drug eruptions. (AGEP: acute generalized exanthematous pustulosis; SJS: Stevens Johnson Syndrome; TEN: toxic epidermal necrolysis; EMM: erythema multiforme major)

Cutaneous drug reactions can be elicited by different immune mechanisms, involving T lymphocytes (T cells, TC), which become activated by antigen-presenting cells (APC) presenting drug allergens (depicted in red) to the T cells, and B lymphocytes (B cells, BC), which are activated by drug-specific T cells. Drug reactions primarily mediated by T cells include maculopapular exanthema, fixed drug eruption, and acute generalized pustulosis (AGEP) as examples of delayed-type hypersensitivity reactions induced by cytokine-producing CD4+ T helper 1 (IFN-γ, TNF-α) or 2 (IL-5) cells and perforin/granzyme B secreting CD8+ T cells or CXCL8- and GM-CSF-producing CD4+ T cells. Severe blistering drug reactions like erythema multiforme (EEM), Stevens-Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN) are mainly mediated by CD8+ cytotoxic T cells releasing granulysin and Fas ligand. On the other hand, B cells are involved in the elicitation of urticaria and angioedema via synthesis of drug-specific IgE antibodies or allergic vasculitis and serum sickness through production of drug-specific IgM, IgG, or IgA antibodies (forming immune complexes triggering the complement cascade in the blood vessels) (Ramdial and Naidoo 2009).

Risk Factors

Often it cannot be explained why someone develops a drug reaction and others do not. A few risk factors have been noted, as gender (two thirds are female), age (adults are more often affected than children), genetic predisposition, concurrent infections, comorbidities, simultaneous intake of several drugs, and summation effects (e.g., anaphylaxis to acetylsalicylic acid only in combination with exercise and/or consumption of alcohol). Also, some drugs are more likely to cause adverse reactions than others. For example, typical elicitors of anaphylaxis are antibiotics, analgesics, contrast media, and monoclonal antibodies; rashes are frequently caused by antibiotics and anticonvulsants; and severe drug reactions like toxic epidermal necrolysis are often provoked by allopurinol, quinolones, or sulfonamides. Finally, repetitive intake of drugs is more likely to induce allergic reactions than continuous exposure.

Clinical Manifestations

Exanthema

Maculopapular or morbilliform exanthema is the most common drug reaction (Fig. 2). While in

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Cutaneous Drug Reactions, Fig. 2 Maculopapular exanthema induced by clindamycin

Cutaneous Drug Reactions, Fig. 3 Fixed drug eruption at the hand

sensitized patients it can occur within 3 days, in patients exposed for the first time to the causative drug and thus first have to become sensitized, it usually takes 8–10 days after the medication was started. The rash usually starts on the trunk and spreads to the extremities, and pruritus may exist. It is a consequence of both CD4+ and CD8+ T-cell activation, which recognize the drug either via presentation by antigen-presenting cells or may be even directly (Shear et al. 2008). They release different cytokines (IFN-γ, TNF-α, IL-5) and cytotoxic granula (granzyme B, perforin) leading to apoptosis of keratinocytes (Fig. 1). Typical elicitors of exanthematic eruptions are antibiotics, anticonvulsants, and allopurinol (Yawalkar 2007). Diagnosis is based on patch test showing delayed-type hypersensitivity sensitization against the suspected drug and/or oral provocation test. A special form is the amoxicillin-induced rash in patients suffering from viral infections like EBV infection. Most likely, the virus serves as an important cofactor, since most of them tolerate amoxicillin in other circumstances.

Fixed Drug Eruption

Fixed drug eruptions present as solitary, round, or oval erythematous macules or plaques of less than 10 cm diameter (Fig. 3), with or without central blister. They are mostly found at the oral mucosa, genitalia or, acral skin. Resolution takes a few days to weeks and often leaves a long-lasting pigmentation. On reexposure to the causative medication, the lesions recur typically at the same location within 30 min to 12 h. This reaction as well as positive responses in patch testing at the side of previous lesions can be explained by an immunologic memory effect due to memory CD8+ T cells residing in the affected skin. Commonly causative drugs are antibiotics, analgetics, and barbiturates.

Acute Generalized Exanthematous Pustulosis (AGEP)

AGEP usually appears 1–3 weeks after drug administration. If a sensitization has already taken place, skin reactions occur within a few days. The clinical picture is characterized by tiny, non-follicular pustules following a rapid onset with erythematous patches, edema, and fever (Fig. 4). Patients typically show leukocytosis with neutrophilia. Mortality due to secondary infections or comorbidities is up to 5 %. However, most patients show a complete resolution after about 2 weeks, often accompanied by a generalized desquamation. AGEP is a T-cell-mediated skin eruption, which presents with a delayed-type hypersensitivity reaction in patch testing. Pathogenetically important is a drug-specific CD4+ T lymphocyte secreting CXCL8 and GM-CSF (Fig. 1), leading to an activation and cutaneous infiltration of neutrophils. Typical elicitors are antibiotics, particularly aminopenicillins and macrolides.

Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)

DRESS is also known as hypersensitivity syndrome. First symptoms normally turn up

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Cutaneous Drug Reactions, Fig. 4 Acute generalized exanthematous pustulosis, showing tiny non-follicular pustules on erythematous patches

between 6 weeks and 3 months after starting treatment with the eliciting drug, a significant difference compared with other cutaneous drug reactions. Most commonly, DRESS starts with temperatures up to 40 °C. A few days later, a maculopapular exanthema occurs, which can pass into erythrodermia. Diagnosis is based on six criteria, namely, rash; fever; generalized lymphadenopathy; systemic organ involvement like hepatitis (about 70 % show increased aminotransferases), nephritis, pneumonia, myocarditis, myositis, arthritis, or pancreatitis; eosinophilia; and leukocytosis with atypical lymphocytosis. Mortality rate is up to 20 %. The pathogenesis is still unknown, but a decrease of immunoglobulins in the beginning of the reaction and a reactivation of human herpes viruses seem to play an important role. Most frequently aromatic anticonvulsants, namely, phenytoin, carbamazepine, and lamotrigine, are causes of DRESS.

Cutaneous Drug Reactions, Fig. 5 Erythema exsudativum multiforme with targetoid lesions composed out of peripherally accentuated erythematous macules, some of them containing a central blister

Erythema Multiforme

Erythema multiforme, also called erythema exsudativum multiforme (EEM), is characterized by targetoid skin lesions and erythematous, edematous macules with peripheral accentuation, sometimes showing a bulla in the center (Fig. 5). That is the way typically targetoid cutaneous lesions are developed. While the minor form is mostly confined to the extremities and typically follows infectious diseases caused by herpes simplex virus or mycoplasma, the major form shows more extensive skin involvement; can involve the oral, ocular, or genital mucosa; and can be accompanied by significant malaise, fever, and arthritis. It can be provoked by drugs and overlaps to SJS and TEN (see below) are possible. However, it may also present the same type of cutaneous drug reaction, which just does not develop into full-blown TEN.

Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN)

SJS and TEN are life-threatening severe adverse drug reactions of the skin and mucous membranes. With one or two cases per one million inhabitants annually, they are rare but the mortality rate is high with up to 35 % (Mockenhaupt 2009). Most frequently, they occur 1–3 weeks after starting a new drug, but at least within the first 2 months of therapy. In rare cases, other reasons (mostly infections) are possible (Hazin et al. 2008). Risk factors

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Cutaneous Drug Reactions, Fig. 6 Involvement of mucous membrane in a patient with TEN due to allopurinol intake

promoting the development of SJS or TEN are HIV infection or a genetic disposition, which then predisposes to severe cutaneous drug reaction against specific drugs like carbamazepine (Thong and Tan 2011; Mockenhaupt 2012). It has been proposed that SJS concerns less than 10 % of the skin and TEN more than 30 %, with involvement of 10–30 % called overlap syndrome. However, on practical grounds these subgroups are difficult to distinguish and might just present a continuum of the same disease. Often it starts with a red rash, on which targetoid lesions and multiple blisters can arise, resembling a second-degree burn. Erosion of the mucosa appears especially on the mouth (Fig. 6) but also on the eyes and genital area. The skin eruptions are accompanied by fever and severe malaise. The complications are dehydration and loss of electrolyte, glomerulonephritis, and infection. The pathogenesis is still a matter of intensive research, but drug-specific cytotoxic T lymphocytes inducing extensive keratinocyte apoptosis via the release of granulysin and Fas ligand (binding to the Fas molecule on keratinocytes) seem to play a major role (Fig. 1) (Harr and French 2012). Soluble Fas ligand has been found in higher concentrations in patient serum with severe drug reactions. Among the most common causative drugs for SJS and TEN are allopurinol, anti-infective sulfonamides, aminopenicillins, cephalosporins, nevirapine, sertraline, anticonvulsants (carbamazepine, phenytoin, phenobarbital, lamotrigine), and oxicam nonsteroidal inflammatory drugs.

Urticaria and Angioedema

Usually within minutes to 1 h after drug administration, urticaria (pruritic wheals of various sizes) and/or angioedema (swellings of the deep dermal and subcutaneous tissues) can develop. The clinical pattern can change, because some urticarial lesions disappear immediately and others develop or coalesce and form plaques. Angioedema is most frequently located in the face, typically unilateral. They are mediated by inflammatory mediators like histamine and leukotrienes, released by mast cell or basophil granulocytes, which can become activated by different mechanisms (Fig. 7). These include the direct liberation (e.g., of histamine by opiates, narcotic analgesics, or contrast media), IgE-mediated immune reactions (e.g., by beta-lactam antibiotics like penicillin), or an intolerance. The later is caused in predisposed individuals by nonsteroidal anti-inflammatory drugs which block the enzyme cyclooxygenase I (like paracetamol, acetylic acid, ibuprofen), thereby favoring the synthesis of leukotrienes by the lipoxygenase in mast cells and basophils. Solitaire angioedema is frequently caused by angiotensin-converting enzyme (ACE) inhibitors, which promote the production of angiotensin and bradykinin.

Vasculitis Allergica and Serum Sickness

Vasculitis allergica is caused by immune complexes of drug antigens with antigen-specific immunoglobulins, which can be of the IgM, IgG, or IgA (in case of Schönlein-Henoch purpura) isotype. These immune complexes are precipitated in the small vessels of the skin (and sometimes also in internal organs like the gastrointestinal or urogenital tract), where they activate the complement cascade and neutrophils, leading to vessel damage and petechial hemorrhage. Another immune complex-mediated drug reaction is serum sickness, characterized by an urticarial rash, fever, and arthralgia.

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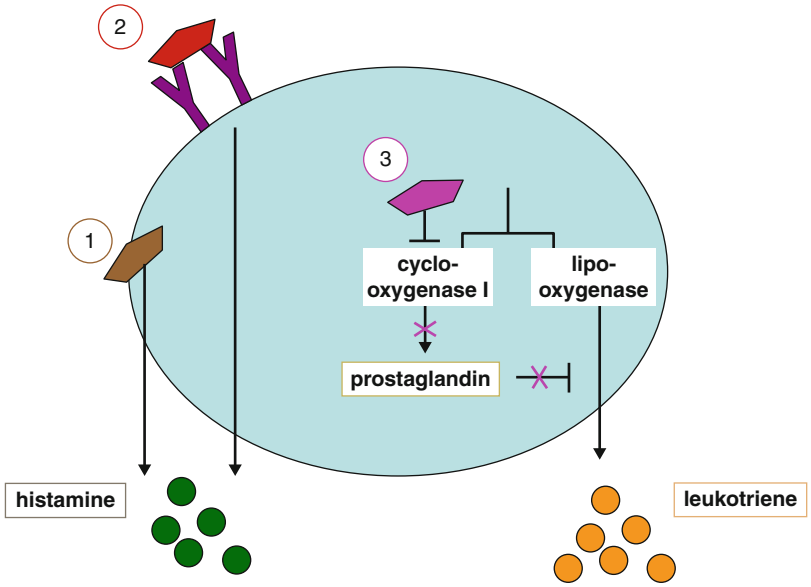

Cutaneous Drug Reactions, Fig. 7 Drug-induced urticaria and angioedema are mediated by the release of different mediators like histamine or leukotrienes from mast cells and basophil granulocytes. Possible mechanisms are either direct cell activation (*1*), immune mediated by binding to drug-specific IgE antibodies (*2*), or interference with the cyclooxygenase pathway (*3*). In the later, nonsteroidal anti-inflammatory drugs, which block the cyclooxygenase I, promote the increased production of leukotrienes in predisposed individuals, since the inhibitory effect of prostaglandins synthesized through cyclooxygenase activation is missing

Other Cutaneous Drug Reactions

Many more cutaneous drug reactions are known (like cutaneous reactions caused by biologics or cytostatic drugs), which are too numerous to be described in detail in this entry.

Diagnosis

The diagnosis of an adverse drug reaction is based on the history and skin tests, if available in vitro tests, and based on the former test results of provocation tests. If a severe cutaneous drug reaction like TEN is suspected, a skin biopsy is required which would show necrosis of the complete epidermis (Mockenhaupt 2009). The medical history consists of the patient's statement and all records and reports about the reaction as well as previous test results. The survey includes known hypersensitivities, atopic diseases, comorbidities, and potential cofactors favoring a drug reaction like infections, alcohol intake, or exercise. Regarding the history of the potential drug reaction, important details are drug ingredients, dosage, time of onset relative to starting the drug, duration of use, and past reactions to the same or structurally related medication.

Skin testing should optimally take place 4 weeks to 6 months after the reaction (Przybilla et al. 2008). For immediate-type skin reactions (urticaria, angioedema), skin prick and intracutaneous tests are recommended; for delayed-type reactions (exanthema, fixed drug eruption, AGEP, DRESS), intracutaneous and patch tests with readings after 48 and 72 h, respectively, and – if supposed to be relevant – photopatch tests should be performed. In case of fixed drug eruption, the test ideally should be performed at the site of the previous reaction, with the first reading at the following day. In case of EEM, TEN, or SJS, no appropriate skin test exists.

In case of immediate-type cutaneous reactions (urticaria, angioedema), patients' serum may be screened for specific IgE antibodies for some drugs. Other potential tests are the basophile activation test (Sanz et al. 2009),

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histamine release test, and the leukotriene release test, all of which include testing of the suspected drugs' ability to activate the patients' basophile granulocytes. For delayed-type cutaneous reactions (exanthema, fixed drug eruption, AGEP, DRESS, may be also EEM, TEN, and SJS), the lymphocyte transformation test, measuring the proliferation of patients' T lymphocytes stimulated with the suspected drug, can be performed (Merk 2005; Przybilla et al. 2008). However, like the skin tests, all these tests only show the patients' ability to react against a drug, but do not prove an allergic reaction, since the patient may only be sensitized against the suspected drug.

In allergy diagnosis, the gold standard is the provocation test, confirming the clinical relevance of positive skin or in vitro tests or proving that a drug is tolerated in case of negative cutaneous or blood tests. However, one always has to balance the potential risk of such a test with the value of its outcome. In some cases just testing alternative drugs is an option. In addition, some drugs cannot be tested without major interventions due to their pharmacological features (i.e., muscle relaxants, which need to put the patient into general anesthesia). If possible, oral uptake of a drug is favored.

Therapy

Suspected drugs should be discontinued. Depending on the intensity of the cutaneous reaction and the presence of concurrent internal organ symptoms, the therapy varies from no treatment via local/cutaneous corticosteroid application to systemic corticosteroids, antihistamines, and in some cases adrenalin. Life-threatening severe adverse drug reactions like SJS and TEN need complex interdisciplinary medical care. Because SJS and TEN are rare diseases, official treatment guidelines do not exist. Therapy with systemic corticosteroid for SJS/TEN is discussed controversially; recently treatment with cyclosporine has been shown effective. Others studies have shown a therapeutic benefit of intravenous immunoglobulins; however, the mortality rate still remains high.

Conclusion

Cutaneous drug reactions encompass a wide spectrum of skin reactions ranging from immediate-type reactions like urticaria and angioedema to delayed-type reactions like exanthema and fixed drug eruption to severe blistering diseases like TEN and SJS. The most common drugs that implicate adverse skin reactions are antibiotics, NSAIDs, anticonvulsants, and allopurinol. Identification and discontinuation of the responsible drug is the most important. To prevent further reactions, the drug and potentially cross-reacting medication should be avoided.

Cross-References

- ▶ Diagnostic Components: Allergen for In Vivo (Skin Testing, Immunotherapy) and In Vitro (Serology) IgE Antibody Testing
- ▶ Urticaria

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D

Delayed Allergic Hypersensitivity to Corticosteroids

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Synonyms

Allergic contact to corticosteroids; Type IV hypersensitivity to corticosteroids

Definition

Allergic contact dermatitis is the most frequent presentation of delayed allergic hypersensitivity to corticosteroids (CCs). However, patients previously sensitized by topical use of CCs may also react upon a systemic administration.

Other forms of delayed allergic hypersensitivity to CCs are generalized dermatitis, exanthema, purpura, and erythroderma (Whithmore, 1995).

Historical Background

The therapeutic properties of CCs were first demonstrated by Hench (Hench et al. 1949). During the 1950s, it was discovered that hydrocortisone, a natural glucocorticoid hormone, could reduce inflammation and proliferation in some skin disorders.

Reichstein and Kendall isolated the hormone of the adrenal cortex. As a result of those findings, the three authors won the Nobel Prize for Medicine in 1950.

Prevalence

The frequency of CC allergy following a topical application ranges from 0.2 % to 5 % (Brandão and Goossens, 2011).

Allergic reactions following systemic administration of CCs have rarely been reported. So its frequency varies in the literature between 0.1 % and 4 %.

Locoregional routes, including respiratory (nasal or mouth inhalation), digestive, and intra-articular administration, have been less frequently implicated.

Pathogenesis

The delayed allergic reactions have classically been described as type IV reactions caused by T cells. In skin biopsies of positive patch test of CC-sensitized patients, they have demonstrated (Baeck et al. 2013) that the inflammatory infiltrated is composed of CD3+ T cells with

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a predominant TH2 cytokine profile that are rapidly recruited, in contrast to studies that have highlighted the role of CD8+ T cells as effector cells in both drug and contact allergies. Moreover, they observed, for the first time in patients with allergic hypersensitivity to CCs, an increase in the number of IL-4-producing γ/δ TCR lymphocytes.

Clinical Manifestations

Therefore, it may appear to be paradoxical that CCs, potent anti-inflammatory agents and immunomodulators used in the treatment of allergic manifestations, are capable of producing allergic hypersensitivity.

The clinical symptoms depend on the administration route.

Allergic contact eczema following a topical application of CCs is far the most common form of delayed hypersensitivity. Although recognizing CC allergy can be difficult, its clinical presentation tends to be neither specific nor spectacular. Therefore, it is important to think in delayed hypersensitivity to CCs if a chronic eczema does not improve with CC treatment.

After systemic administration of CCs, delayed allergic hypersensitivity reactions are generalized dermatitis, exanthema, purpura, or erythroderma, often associated with bullae.

Furthermore, CC allergy can induce an allergy to endogenous progesterone, for which the clinical presentation is a generalized eczematous eruption which gets worse during the premenstrual period.

Diagnosis

Type IV hypersensitivity can be identified by skin tests, mainly patch tests. But we can also use intradermal tests with late readings with CC suspensions diluted, if the prick tests are negative (Padial et al. 2005; Corominas et al. 2007).

Using baseline patch tests, the principal markers for CC contact allergy are tixocortol pivalate, budesonide, and hydrocortisone 17-butyrate. The vehicle used is petrolatum except for ethanol in hydrocortisone because of its weak transepidermal penetration.

There are also commercial batteries of patch tests with different usual CCs.

False-negative tests can result because of the anti-inflammatory properties. So, delayed patch test reading on day 7 (D7) or even later should be implemented to avoid concealed allergens (Subramanian et al. 2006).

The anti-inflammatory properties of CCs also lead to the "edge effect" (Baeck et al. 2009): a ring of induration, erythema, and/or papulovesicles around the patch test site, with no reaction in the center. The phenomenon can be explained by a higher concentration of CCs in the center of the patch, where there is therefore a more powerful anti-inflammatory effect.

Another problem frequently encountered is the initial period of vasoconstriction "skin blanching" (and the attendant risk of a false negative) followed by massive vasodilation with marked erythema (and the attendant risk of false positive).

It is also important to test other active principles in topical CC treatments (creams, lotions, eyedrops, etc.) (Jacob and Herro, 2013), vehicles, and preservatives present in the preparations used. The allergens most often associated with topical CCs are neomycin, propylene glycol, wool alcohols, benzyl alcohol, formaldehyde, imidazolidinyl urea, diazolidinyl urea, paraben mix, fragrance mix, myroxylon, and other sorbitan derivatives (Asarch and Scheinman, 2008; Coloe and Zirwas, 2008; Cressey et al. 2012).

Allergy to additives, such as sodium carboxymethylcellulose, a semisynthetic hydrosoluble polymer, with high molecular weight which is used as an excipient in numerous injectable CC preparations, especially intra-articular solutions, should also be ruled out.

Other additives used in intradermal tests are monosodium phosphate and disodium phosphate included in commercial preparations.

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If the tests are negative, a repeated open application test (ROAT) twice a day during 7 days should be done, before a diagnosis of delayed hypersensitivity to CCs.

Cross-Reactions

In 1989, based on structural and clinical characteristics, Coopman et al. classified CCs into four reactivity groups, namely, groups A, B, C, and D. In 1995, Lepoittevin et al. observed that cross-reactivity among CCs supported this classification. Nevertheless, a pure structural analysis of CCs does not justify the existence of the group C.

According to Baeck et al. (2011), the new groups are:

Group 1	Group 2	Group 3
Budesonide	Amcinonide	Alclomethasone dipropionate
Cloprednol	Desonide	Beclomethasone dipropionate
Cortisone acetate	Fluchloronide	Betamethasone
Diclorisone acetate	Flumoxonide	Betamethasone 17-valerate
Difluprednate	Flunisolide	Betamethasone dipropionate
Fludrocortisone acetate	Fluocinolone acetonide	
Fluprednisolone acetate	Fluocinonide	Betamethasone sodium phosphate
Fluorometholone	Halcinonide	Clobetasol propionate
	Triamcinolone acetonide	Clobetasol butyrate
Hydrocortisone	Triamcinolone	Desoxymethasone
Hydrocortisone aceponate	Triamcinolone benetonide	Dexamethasone
Hydrocortisone acetate	Triamcinolone diacetate	Dexamethasone acetate
Hydrocortisone 17-butyrate	Triamcinolone hexacetonide	Dexamethasone sodium phosphate
Hydrocortisone 21-butyrate		Diflucortolone valerate
Hydrocortisone hemisuccinate		Diflorasone diacetate
Isoflupredone acetate		Flumethasone pivalate
Mazipredone		Fluocortin butyl
Medrisone		Fluocortolone
Methylprednisolone aceponate		Fluocortolone caprylate
Methylprednisolone acetate		Fluprednidene acetate
Methylprednisolone hemisuccinate		Halomethasone
Prednicarbate		Meprednisone
Prednisolone		Fluticasone propionate
Prednisolone caproate		Mometasone furoate
Prednisolone pivalate		
Prednisolone sodium metasulphobenzoate		
Prednisolone succinate		
Prednisone		
Tixocortol pivalate		
Triamcinolone		

Corticosteroids with a greater capacity to bind to arginine do have stronger allergenic properties. CCs without fluorine substitution experience more rapid metabolic degradation and therefore bind more easily to arginine than their fluorinated derivatives and hence are more likely to induce allergic reactions.

Management

If there is a diagnosis of delayed allergic hypersensitivity to CCs, they should be avoided. However, there are patients who react to molecules from one unique group and patients who may react to the entire spectrum of CCs, so probably there are different areas of immune recognition. Therefore, a correct diagnosis and controlled administration test to study any possible cross-reactivity should be needed. Corticosteroids are often essential drugs, and the use of substitutes is not always available.

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Cross-References

- ▶ Allergic Contact Dermatitis
- ▶ Fragrancy, Allergic Contact Dermatitis
- ▶ Methods (In Vivo): Skin Test (Intradermal, Puncture)
- ▶ Topical Corticosteroids

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Delayed Anaphylaxis to Mammalian Meat (Alpha-Gal)

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Synonyms

Alpha-gal; Alpha-galactose; Galactose-alpha-1,3-galactose IgE

Definition

Galactose-alpha-1,3-galactose (commonly referred to as alpha-gal) is a carbohydrate present on nonprimate mammalian tissue. This carbohydrate can trigger delayed anaphylaxis, which occurs 3–6 h following the ingestion of mammalian meat, including beef, lamb, or pork (Commins et al. 2009).

Background: Alpha-Gal and Cetuximab

The role of the alpha-gal carbohydrate in anaphylaxis was first discovered in a population of patients who were experiencing an abnormally high rate of allergic reactions to cetuximab, even during administration of the very first dose (Commins and Platts-Mills 2009). Cetuximab is a monoclonal antibody that is approved for treatment of certain cancers and was reported to have an incidence of severe allergic reactions in approximately 3 % of patients (Chung et al. 2008). However, several studies indicated higher

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rates of allergic reactions in southeastern states, with cases reported in Arkansas, Georgia, Kentucky, Mississippi, Missouri, North Carolina, Oklahoma, Tennessee, Texas, South Carolina, Virginia, and West Virginia (Commins and Platts-Mills 2010). In particular, one study of patients in Tennessee and North Carolina showed 22 % of patients experiencing severe allergic reactions, often with the first exposure to cetuximab (O'Neil et al. 2007). In 2008, it was discovered that these reactions were mediated by preexisting IgE antibodies to cetuximab (Chung et al. 2008). These IgE antibodies were specific for the carbohydrate alpha-gal, which is present on cetuximab, but also on a variety of mammalian proteins, including cat, dog, beef, pork, and lamb (Commins and Platts-Mills 2009).

Why the Delay?

While the allergic reactions to cetuximab manifest quickly, often during the infusion of the medication, reactions to mammalian meat tend to be delayed up to 3–6 h. This would suggest that some process is delaying the presentation of the carbohydrate to immune system. Normal digestion of carbohydrates is not only rapid but would likely result in cleavage of the alpha-gal carbohydrate. Therefore, it is hypothesized that these carbohydrates are absorbed in the form of glycolipids that are incorporated into chylomicrons, which are then released into the circulation where they may trigger histamine release. The increased length of time required for lipid absorption and chylomicron processing would account for the delay in manifestation of allergic symptoms. This theory has been supported by anecdotal evidence that meat with greater fat content is more likely to trigger severe reactions (Commins and Platts-Mills 2010).

Alpha-Gal and Ticks

Several studies performed in Australia and Virginia describe an association between a history of tick bite reaction and mammalian meat allergy, which was confirmed by screening sera of patients both before and after tick bites. Tick proteins are known to be immunogenic, and it is hypothesized that these tick bites may represent the first exposure to alpha-gal carbohydrates that trigger the formation of IgE. This would explain why many of the patients with cetuximab allergy have preexisting IgE to alpha-gal and react upon their first exposure to cetuximab. Additionally, the regional distribution of delayed anaphylaxis to mammalian meat in the southeastern states coincides with the distribution of American ticks (Commins and Platts-Mills 2009). In the southeastern United States, the *Amblyomma americanum* tick has been implicated in this process; however, in other European countries and Australia, other ticks are thought to cause sensitization to alpha-gal. Patients with delayed anaphylaxis to alpha-gal tend to experience severe local reactions to tick bites, which often present in one of three basic patterns. Some report severely pruritic reactions that last weeks to months due to a few tick bites from adult ticks. Others report intermittent repeated bites, often associated with increased tick exposure from their occupation or hobbies. The third group describes intensely pruritic larval tick bites, which present in groups of 10–100 bites, persist no more than a few weeks, and are often mistaken for chigger bites (Commins et al. 2011).

Diagnosis of Alpha-Gal Allergy

Patients with delayed anaphylaxis due to mammalian meat will describe an onset of symptoms generally 3–6 h after the ingestion of the trigger (beef, lamb, pork), in contrast to traditional anaphylaxis which often manifests within minutes and always within 2 h. Symptoms can vary in severity ranging from isolated hives or swelling to full-blown anaphylaxis, including lower-airway obstruction and signs of shock. Patients do not report reactions in response to chicken, turkey, or fish. This allergy also differs from traditional allergies in that it often begins in adult life (Commins and Platts-Mills 2009).

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As described above, it is also useful to ask patients about a history of excessive local reactions to tick bites or chigger bites. Patients may also report variability in the forms of mammalian meat that trigger a reaction, specifically, worse reactions to meats with greater fat content (Commins and Platts-Mills 2010).

Performing skin prick testing for beef, pork, or lamb on patients with alpha-gal-specific IgE produces weak responses, with wheals that are generally less than 4 mm. Skin prick testing with freshly prepared meat extracts or intradermal testing can provide larger responses. In contrast, IgE-specific tests to beef, lamb, pork, or the alpha-gal carbohydrate are more reliable (Commins and Platts-Mills 2010). Patients may also have IgE specific to cow's milk, dog, and cat. Fish- and poultry-specific IgE are not found in association with alpha-gal allergy (Commins et al. 2009).

Differential for Delayed Anaphylaxis to Mammalian Meat

There are other etiologies of meat-induced allergy and anaphylaxis that may be confused with alpha-gal allergy. Some patients produce IgE specific to certain epitopes on serum albumin that are similar in both cat and pork, which is known as pork-cat syndrome. Other patients who are allergic to cow's milk can have symptoms with ingestion of beef due to cross-reactivity between beef and cow's milk proteins. These cross-reactions are not due to the alpha-gal carbohydrate and do not manifest with delayed symptoms (Commins and Platts-Mills 2009).

Management of Delayed Anaphylaxis to Mammalian Meat

Currently, the recommendation for alpha-gal allergic patients is to avoid all mammalian meat. While some patients occasionally tolerate small amounts of meat, they often will experience severe life-threatening reactions later to an equally small amount of a different meat. As it is unknown what factors affect the likelihood of severe reactions, it is advised that they avoid mammalian meat completely. Allergic reactions to mammalian meat should be treated with standard management, including antihistamines and intramuscular epinephrine when appropriate (Commins et al. 2009). Of note, in patients with IgE specific for alpha-gal who require cetuximab, desensitization has been successfully performed in small numbers (Commins and Platts-Mills 2009).

Cross-References

- Cow's Milk Allergy
- Diagnostic Components: Allergen for In Vivo (Skin Testing, Immunotherapy) and In Vitro (Serology) IgE Antibody Testing
- Food Allergens
- Food Allergies, Diagnostic Testing
- Food Allergy, Overview
- Methods (In Vivo): Skin Test (Intradermal, Puncture)

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Dendritic Cells

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Synonyms

Alveolar; DC subtype "A" cells; IDDC; Inflammatory; Langerhans; Plasmacytoid; Resident

Definition

Dendritic cells (DCs) are immune cells sparsely distributed in the tissues of organs (e.g., skin, lung, gut) that are especially adapted in acting as "sentinels" that capture and process antigen from the environment for presentation to T lymphocytes. In doing so, they possess professional antigen-presenting cell (APC) activity that plays a critical role in activating naïve T cells for initiating and maintaining adaptive immune responses. DCs have become recognized as providing a critical link between the innate and adaptive arms of the immune system.

Historical Background

Ralph A. Steinman and Zanvil A. Cohn are credited with first coining the name "dendritic cells" in 1973 after identifying a rare cell (<1 % of adherent cells) from the spleen of mice that became irregular in shape and formed dendrite-like protrusions in culture (Steinman and Cohn 1973). Paul Langerhans had described the appearance of similar cells (Langerhans cells) before the turn of the twentieth century, as did others with the description of the so-called "A" cells in the late 1960s (Rowley and Fitch 2012). Nonetheless, Steinman and colleagues are credited with much of the early work regarding the in vitro and in vivo function of DC. This includes the first evidence that these cells are responsible for inducing the T cell responses observed in mixed leukocyte reactions (MLR). The plethora of work that followed, and conducted by many investigators, has since shown that DCs play a critical role both in the initiation of immune responses and in the induction of peripheral tolerance (Steinman 2012).

Functional Responses

While many kinds of DC have been described and are known to differ in origin, anatomic location, and function, two main lineages are commonly recognized. DCs of myeloid origin, which typically bear CD11c along with MHCII, constitute the largest group and are themselves composed of many subpopulations that vary widely in marker expression among mice vs. man (Banchereau et al. 2000; Vermaelen and Pauwels 2005). Plasmacytoid dendritic cells (pDC), so-called because of their resemblance to lymphoid plasma cells, are CD11c negative and are the sole member of the other major DC subtype. Naturally, the primary function of both DC subtypes upon capturing antigen is to migrate to lymphoid tissue in order to present processed peptides to reactive lymphocytes and initiate primary immune responses. However, Liu and colleagues showed in the late 1990s that immature pDCs circulating in the blood constitute a rapid and major source of type I interferons (e.g., IFN-alpha/beta) (Liu 2005). This prompted the notion that individual DC subsets are additionally designed to bring about quick, yet specific, innate immune responses to the wide range of self and nonself components they may encounter. In the instance

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of IFN-alpha/beta secretion by pDCs, this most certainly represents a first-line immune response to viral components. Indeed, large quantities of type I IFNs are produced by pDCs as a result of these cells recognizing viral nucleic acid sequences interacting with the intracellular Toll-like receptors (TLR)-7/9 expressed in these cells. Unmethylated CpG-DNA is specifically recognized by TLR9, whereas TLR7 binds single-stranded RNA (ssRNA). In contrast, many myeloid DC populations, both in humans (referred to as mDC) and in mice (referred to as conventional DC, cDC), are known to produce IL-12 when exposed to microbial ligands (e.g., LPS = lippolysaccharide) that interact with TLR4 expressed on these subtypes.

The exact nature of how immature DC subtypes respond to innate immune stimuli has become an important topic in determining how adaptive immune responses evolve (Steinman 2012). This is because dendritic cell maturation is a critical link between innate and adaptive T cell-dependent immunity, and cytokine production by DC is an important initial step in the maturation process (Banchereau and Pascual 2006). For example, there is a body of evidence that immature human pDCs, if first exposed to CpG (via TLR9) or ssRNA (via TLR7), mature into APCs that are better at promoting Th1 responses. IFN-α may very well play a role in this response, since this type I IFN is known to suppress Th2 development (Huber et al. 2010). In contrast, immature pDCs also express a variant of the high-affinity receptor for IgE (FcεRI). Studies have shown that cross-linking of specific IgE bound to this receptor (perhaps resulting from the binding of allergen) suppresses TLR7/9-dependent IFN-α responses in pDCs and thus the anti-Th2 activity mediated by this cytokine (Schroeder et al. 2005; Schroeder et al. 2008; Gill et al. 2010). Therefore, this interaction involving FcεRI/IgE could instead have an important role in sustaining the Th2 responses that are hallmark in allergic disease. In support of this observation, several reports have concomitantly demonstrated impaired TLR7/9-dependent IFN-α production among pDCs isolated from allergic subjects, which theoretically occurs with chronic exposure of allergen-binding specific IgE (Tversky et al. 2008; Gill et al. 2010). It therefore seems appropriate to conclude that a better understanding of DC maturation could provide additional insight into therapies/vaccines that favor a beneficial immune response (see below).

The rarity of DC and the difficulties in isolating these immune cells initially complicated studies investigating their function. However, methods evolved for growing and/or differentiating expanded numbers of DC subtypes from precursor cells, which also provided insight regarding the growth factors important to do so (Steinman 2012). For example, GM-CSF and IL-4 (or IL-13) are critical growth factors for differentiating PBMC-isolated monocytes into DCs, and this approach is used extensively to study human DCs of myeloid origin. Flt-3 ligand is another growth factor and is often used in growing DC from bone marrow precursors.

Emerging evidence is revealing that epithelial cells in various anatomic locations (e.g., skin and airways) are themselves quite instructive in determining how DCs mature into APCs that initiate T cell responses (Pulendran and Artis 2012). For example, the growth factor TSLP (an IL-7-like cytokine) induces OX-40 L expression on mDCs, which, in the absence of IL-12, is critical for development of the Th2 phenotype during antigen presentation to naïve T cells. Both IL-33 (an IL-1-like cytokine) and IL-25 (also known as IL-17E) may additionally promote this polarization toward the Th2 phenotype.

Immunophenotypic Markers

Dendritic subtypes, both in humans and mice, express a variety of phenotypic markers that help distinguish these populations from one another. DEC205 is a common marker found on mouse cDC and is one of the first identified, along with CD11c (Steinman 2012). Mouse cDCs are typically $CD8^+$, whereas mouse pDCs are $CD4^+$. B220 (a B cell lineage marker) and Ly6c (a T cell activation antigen) are lineage-specific markers found on mouse pDC (Liu 2005). In humans, pDCs are readily identified as $CD4^+$, $CD123^+$, $CD11c^-$, $CD303^+$ (blood dendritic cell antigen

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{BDCA}2), and $CD304^+$ ($BDCA\text{-}4^+$) cells. BDCA-4, which is also known as neuropilin-1, is often targeted in isolating pDC from blood (Dzionek et al. 2000). Human mDCs are also $CD4^+$ but $CD123^{low}$, $CD11c^+$, and CD1c $(BDCA\text{-}1)^+$. MHC II is highly expressed on immature DC and is increased more so on mature DC. Immature human pDCs from blood express no to little co-stimulatory molecules (e.g., CD80/86), but these markers are increased upon in vitro maturation (e.g., by IL-3 or TLR7/9 agonists). Interestingly, human mDCs isolated from blood express relatively high levels of CD86 but no CD80 (Le et al. 2009). Both molecules are increased with maturation of this DC subtype. Immature DCs in blood generally express specific chemokine receptors (e.g., $CCR1\text{-}6^+$, $CXCR1^+$, $CXCR4^+$) that are important for migration to epithelial tissue surfaces, whereas other receptors (e.g., CCR7) are thought to play a critical role in the migration of these cells to lymphoid tissue (Vermaelen and Pauwels 2005).

Many so-called pathogen-associated molecular pattern (PAMP) receptors are expressed on DC, with TLR receiving substantial attention in recent years. As noted, mDCs generally express high levels of cell surface TLR2/4, but can also show intracellular TLR3/8 expression (ligands: double-stranded and single-stranded RNA, respectively). pDCs express intracellular TLR7/9. With regard to FcεRI expression, both the pDC and mDC subtypes in humans express the $\alpha\gamma_2$ variant of this receptor (Novak et al. 2010). This receptor is implicated in allergen presentation and, like the $\alpha\beta\gamma_2$ variant expressed on mast cells and basophils, is driven by serum IgE levels. Expression of FcεRI on mouse DCs remains controversial.

Dendritic Cell-Based Therapies

With dendritic cells now viewed as central players in initiating antigen-specific immunity and tolerance, their involvement in many immune-based medical conditions has likewise become imperative (Steinman 2012). This is evident not only for infections but also for autoimmunity (e.g., juvenile diabetes, multiple sclerosis), transplantation, asthma/allergies, cancer, atherosclerosis, and bone disease. As a result, there is substantial effort toward the development of therapies that target and/or manipulate DC function in order to facilitate a beneficial immune response. One strategy being tested involves targeting antigen to specific DC subtypes by coupling it with DC-specific ligands (e.g., HIV gag p24) or with antibodies that target specific DC markers (e.g., DEC-205). Other approaches focus on coupling antigens to adjuvants that not only target specific DC subtypes but also prime these APCs to induce precise T cell responses. For example, one of the first attempts of this approach was the use of the so-called allergen immunostimulatory conjugate (AIC), or TOLAMBA™, made by Dynavax Corporation as a vaccine for treating ragweed-induced hay fever. AIC consisted of amb a 1 (the major allergen of ragweed) conjugated with DNA oligonucleotides containing unmethylated CpG motifs that target pDCs (and B cells) expressing TLR9. Preclinical testing in mice had showed that this compound induces potent Th1 responses while suppressing Th2-associated responses including IgE. A small double-blind placebo-controlled study in 24 human subjects showed that with just 6 weekly preseason injections, AIC significantly reduced hay fever symptoms during the first but also the following year ragweed seasons (Creticos et al. 2006). More recent strategies are investigating the use of TLR7-specific adjuvants for similar activity (Matesic et al. 2012). It therefore seems certain that the success of such adjuvant-based therapies will advance but only with a greater understanding of how DC maturation/function is affected by specific innate vs. adaptive immune stimuli.

Cross-References

- ▶ Allergen Immunotherapy, Overview
- ▶ Immunomodulator Therapy of Asthma
- ▶ Induction of IgE Synthesis: Cellular Interactions and Molecular Events

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Dermatitis from 2-*N*-Octyl-4-Isothiazolin-3-One, Allergic Contact

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Synonyms

2-*N*-octyl-4-isothiazolin-3-one; Contact dermatitis

Definition

2-*N*-octyl-4-isothiazolin-3-one is an antimicrobial agent used as a preservative in paints, cooling lubricants, and other metal-working fluids. It is a weak sensitizer, which elicits delayed-type hypersensitivity reactions mainly in industrial workers. Sensitized people develop occupational contact dermatitis, often on their hands, but there have been also reports about textile dermatitis due to residues in colored clothes.

Cross-References

► Allergic Contact Dermatitis

Diagnostic Assay Components

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Synonyms

Antibody; Antigen; Buffer; Conjugate; Matrix; Substrate

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Definition

Diagnostic assay components encompass all the individual reagents (antigens/ligands, antibodies/receptors, buffers, labels, conjugates, substrates, calibrators/standards, test specimens), supplies (pipettes, plasticware), and equipment/instrumentation (pipettes, readers) that are required to perform a laboratory immunoassay which quantifies the level or concentration of an analyte in a specimen.

Introduction

At its root, the immunological reaction used in laboratory immunoassays involves an antigen or a foreign substance that elicits the production of antibodies by an organism and an antibody that exhibits specificity for the epitope site on the antigen that it binds (Berson and Yalow 1968). They interact in a vessel or on a surface [plastic (polyethylene) or glass tube, plastic microtiter plate well, plastic stick, polyethylene cap with an internal sponge matrix, and carbohydrate filament-coated silicone chip, cuvette, flow cell, and gel that involves fluid movement]. The fluid environment contains salts that buffer its pH and ionic strength in a physiological range, which promotes antigen–antibody interactions. As the concentration of the antibody added to the reaction mixture increases, the diagnostic assay components first pass through an antigen excess condition which produces small immune complexes where antibody is saturated with antigen molecules. With increasing antibody concentrations, a point of maximal antigen–antibody cross-linking occurs. This region is called the equivalence zone, where precipitin reactions become visible in a gel (see ▶ Analytes and Biomarkers: Precipitin Antibodies) and nephelometers and turbidimeters experience maximum light scatter [see ▶ Methods (in vitro and in vivo): Nephelometry and Turbidimetry]. As the antibody concentration moves further into molar excess over the quantity of antigen, the immune complexes become increasingly smaller, with fewer antigens bound to the gross excess of antibody binding sites.

Specimen Matrix Considerations

A carrier or irrelevant protein is commonly added to the assay buffer to prevent nonspecific binding of the analyte to other specimen components and surfaces of the reaction vessel (see ▶ Assay Performance Parameters). The analyte is the constituent or component of the test and reference calibrator that is measured by the assay. Analytes can include any element, ion, compound, substance, factor, infectious agent, cell, organelle, activity (enzymatic, hormonal, or immunological), or property of the specimen. A qualitative assay is designed to detect the presence or absence of the analyte. In more quantitative assays, the concentration, intensity, or biological activity of an analyte in the specimen is determined, often by interpolation of response data from a reference dose–response or calibration curve. For the diagnostic allergy laboratory, allergen-specific IgE molecules can be considered the primary analyte of interest (see ▶ Analytes and Biomarkers: IgE), and this will be used as a model for illustration. If the matrix of the specimen is insufficiently optimized to reduce nonspecific interactions of the analyte, either because of specific or nonspecific attraction for the walls of the reaction vessel, then the assay may generate a false positive response. For instance, this may occur in the current allergen-specific IgE assays if the total serum IgE exceeds a certain level (e.g., 20,000 kUa/L) such as can occur in the serum of a patient with hyper-IgE syndrome (Matsson et al. 2008). Specificity of this interaction of the analyte (antigen) with antibody can be verified using a competitive inhibition in which either simultaneous or sequential addition of soluble antigen to the reaction vessel inhibits the binding of antibody to its relevant immobilized antigen (see ▶ Assay Performance Parameters). The matrix of the biological specimen varies with the type of specimen. Human serum, urine, saliva, and other secretions or body fluids each have their distinct protein matrix that needs an identical negative control to assess the nonspecific binding levels for each individual diagnostic assay. Other specimens that are occasionally analyzed include

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tear fluid, bronchial or nasal lavage fluid, sputum, cerebral spinal fluid, and cell supernatants. Assays that demonstrate non-parallelism between the calibrator and test specimen dilutions often have mismatched protein matrix-related effects that can become exacerbated if less blood than is required for the collection device is drawn from the patient. Hemolyzed, icteric, or lipemic serum/plasma specimens represent a potential nonspecific binding concern for assays because of their high levels of hemoglobin, bile, or lipid content that alters the specimen matrix composition.

Analyte

Another key component of immunologically based diagnostic assays is the analyte which can be either an *antigen* or as in the illustration for a diagnostic allergy test, an allergen-specific IgE *antibody*. To detect antigen, an immobilized or labeled antibody that has specificity for the antigen is used. To detect and quantify the level of allergen-specific IgE antibody in a specimen, an immobilized or labeled allergen is used.

An allergen is an immunogen that when introduced into a host, induces the formation of IgE antibodies. Native allergen can be extracted from naturally occurring raw pollens, animal hair and epidermal allergens, foods, mold cultures venoms, drugs, or other biomaterials (Matsson et al. 2008). Alternatively, it can be produced using DNA techniques as a recombinant protein. The allergen extract is a complex mixture of molecules, typically containing, proteins, glycoproteins, lipoproteins, or protein-conjugated chemicals/drugs. These have been solubilized from defined (usually biological) sources, and a portion of these molecules elicit an IgE antibody response in exposed and genetically predisposed persons. The allergenic epitope is the submolecular structure on the allergen that is responsible for IgE antibody binding. The allergenic material is then configured into an assay reagent which is the component of the IgE antibody assay that contains allergen either bound to a solid phase (immobilized allergen or allergosorbent) or in solution phase (liquid allergen). Ideally, the allergen reagent should contain all of the allergenic epitopes of that specificity that elicit IgE antibodies in humans so that the complete IgE antibody response is detected.

Calibrator and Controls

In an IgE antibody assay, two types of calibrators have been used (Hamilton 2010; Matsson et al. 2008). The homologous reference serum contains a defined quantity of IgE antibody that binds to the same allergen specificity. Alternatively, as is the case with the current clinically used IgE antibody assays, a heterologous calibrator is used to provide a reference curve from which unknown response data can be interpolated into estimates of IgE antibody quantity. The heterologous calibrator is a serum containing a known quantity of total IgE that is captured with an immobilized antibody specific for the IgE Fc region. This is considered a heterologous calibrator because it is used to establish a dose–response curve from which antibody bound to immobilized allergen (allergosorbent) are interpolated. The heterologous calibrator produces a universal reference curve that can be used to interpolate IgE antibody specific for any of over 150 allergen specificities. The quantities of the total IgE in the heterologous calibrator are defined within limits through direct comparison with a national or international reference material (Butler and Hamilton 1991).

A control specimen allows the investigator to confirm that the assay is performing properly and it verifies the validity of the calibration–reference curve, the assay reagents, and required equipment. A negative control contains all the same components as in the test sample matrix except it is negative for the analyte being measured. For an IgE antibody assay, this would be a serum from a nonallergic (non-atopic) person that is allergen-specific IgE antibody negative. The positive control, in contrast, is a preparation or pool of collected human serum that contains a defined

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level of the analyte (allergen-specific IgE) that has been documented by multiple previous analyses. The negative and positive control sera need to possess a protein matrix analogous in ionic charge, density, pH, and protein content to that of the test specimen to minimize the risk of non-parallelism (see ▶ Assay Performance Parameters). Typically, a range of values (2 standard deviations, 95% confidence interval) are computed for the control specimen in at least ten previous assays, and values in or outside this confidence interval are used in Levey-Jennings quality control charts to identify assays that are in or out of control.

Receptors

The most widely used receptor in immunological assays is antibody. The term antibody describes a family of Y-shaped protein molecules that are produced by B cells as a primary immune defense against an antigenic challenge. Each antibody from a single clone of B cells has an identical pair of binding sites that can combine with its complementary site on an antigen, thereby signaling other immune defenses. An antiserum used in an assay is comprised of a population of molecules, each member of which is capable of binding to a specific antigenic determinant. This population of antibodies contains individual antibody molecules that are monospecific for a given antigen. However, they may also exhibit idiospecific, heterospecific, polyspecific, or unwanted specificity that can occur as a result of cross-reactions with structurally similar antigenic epitopes (see ▶ Assay Performance Parameters). Cell surface receptors and DNA and RNA aptamers have also been used as specific binding reagents in some diagnostic assays.

Conjugate

The conjugate is the assay reagent that is produced by covalently attaching two (or more) substances to each other such as an antibody with a biolabel (enzyme [horseradish peroxidase, alkaline phosphatase] or biotin), radiolabel, or fluorophor. In the case of the allergen-specific IgE assay, a labeled antihuman IgE reagent that binds to the Fc region of the epsilon heavy chain is used to detect IgE antibody that is bound to either an immobilized anti-IgE in the calibration portion of the assay or immobilized allergen in the test portion of the assay. For enzyme-labeled anti-IgE based assays, a substrate is added to the final assay reaction that produces a colored, fluorescent, or chemiluminescent product which is in turn detected with an instrument. The amount of signal or response detected in the final reaction is proportional to the amount of anti-IgE conjugate which is proportional to the amount of allergen-specific IgE antibody in the original serum. This proportionality is critical to quantitative assays and thus it is important that assay demonstrate linearity by which the calibrator dose–response curve and the dilution curve of unknown test specimens dilute out in parallel.

Other Components

Once the assay reagents are optimized, accurate performance of an assay relies on reproducibly produced supplies (plasticware), quality-controlled equipment (pipettes), and validated instruments (gamma counter, colorimeter, fluorometer). Laboratory licensing requirements mandate maintenance and validation of the equipment and instruments on a routine basis with detailed records of preventative maintenance examinations.

Summary

Multiple components are required for the diagnostic immunoassay to function. These include antigens, antibodies, buffers, labels, conjugates, substrates, calibrators/standards, and test specimens. Each of these diagnostic assay components is optimized to maximize the working range of the assay while minimizing nonspecific binding, assay variability, and protein matrix effects that lead to non-parallelism.

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Cross-References

- Analytes and Biomarkers: IgE
- Assay Performance Parameters
- Cow's Milk Allergy
- Diagnostic Assay Components
- Egg Allergy
- Food Allergies, Diagnostic Testing
- Food Allergy, Overview
- IgE Testing
- Imported Fire Ant Allergy
- Peanut Allergy

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Diagnostic Components: Allergen for In Vivo (Skin Testing, Immunotherapy) and In Vitro (Serology) IgE Antibody Testing

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Synonyms

Allergen extract

Definition

Allergen is a foreign substance (antigen) that has the capacity to induce specific IgE antibody production and mediate type 1 hypersensitivity reactions in sensitized (IgE antibody positive) individuals.

Introduction

The diagnosis of human allergic disease depends on verification of sensitization (IgE antibody positivity) using in vivo methods in which allergen is introduced into the skin (see Methods [in vivo]: Skin Test [intradermal or puncture]) and in vitro methods in which IgE antibody is detected in the blood (see Methods (in vitro): singleplex immunoassay autoanalyzers). The key component that allows both in vivo and in vitro assays to detect IgE antibody is the *allergen*-containing reagent (Matsson et al. 2008). Allergens can be broadly categorized at several levels (Table 1). First, they can be subdivided according to their mode of introduction into the body: aeroallergens are inhaled, food allergens are ingested, and venoms or drugs are injected. Some allergens are adsorbed through the skin, and these more commonly lead to type IV (delayed-type) hypersensitivity. The emphasis of this entry will focus on allergen sources that elicit immediate-type hypersensitivity reactions and which are IgE antibody-mediated and not on delayed-type hypersensitivity which is cell-mediated. Further categorization can subdivide allergens into subgroups. The inhaled aeroallergens encompass allergenic components from pollens, molds and yeasts, epidermal and animal proteins and dust mites, and selected airborne chemicals that bind or haptenize onto human serum albumin following adsorption through mucosal surfaces of the lung. The ingested allergens are released from a large group of foods that are consumed and select parasites that colonize the gastrointestinal tract. Injected allergens include Hymenoptera venoms and drugs. The formulation and extent of quality

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Diagnostic Components: Allergen for In Vivo (Skin Testing, Immunotherapy) and In Vitro (Serology) IgE Antibody Testing, Table 1 Illustrative categories of allergens

I. Inhaled allergens
A. Pollens
1. Grasses
2. Weeds
3. Trees
B. Epidermal and animal proteins
C. Molds and yeast
D. Dust mites
E. Insects
F. Chemicals
II. Ingested allergens
A. Foods
B. Parasites
III. Injected allergens
A. Venoms
B. Drugs
IV. Miscellaneous allergens
A. Occupational allergens

documentation and quality assurance differs extensively whether allergenic materials are used in in vivo tests for diagnostic and therapeutic applications or if they are used in vitro for serological identification of IgE antibody.

Nomenclature

There are several hundred substances in indoor and outdoor environments that can induce an allergic response in a previously sensitized individual. Allergen nomenclature in current use is defined by the World Health Organization and International Union of Immunological Societies (WHO/IUIS) Allergen Nomenclature Sub-committee. In 1984, this committee established a general system for nomenclature of allergens based on the Linnaean system which utilizes its scientific name that includes the first three letters of the genus, first letter of the species, and a number to define the allergen (Marsh et al. 1986; King et al. 1994). If there is an isoallergen variant, it is given a four digit number. The family and order in which the allergenic substance resides must also be defined. Overviews of the evolutionary stages in the establishment of allergen nomenclature system are presented elsewhere (Larsen and Lowenstein 1996; Chapman 2004). Increasingly, allergen nomenclature is linked with the structural biology, function, and extent of immune response induction of the particular allergen (Chapman et al. 2007).

In submitting a new allergen for consideration of inclusion in the WHO/IUIS list of defined allergens, a number of physical, chemical, and immunological properties must be determined. These include the allergen source, proposed allergen name, biochemical name, whether it has been expressed as a recombinant protein including the organism and vector, its molecular weight and how the molecular weight was defined, whether there are any post translational modifications such as glycosylation, and its molecular biology (sequence and structure accession number). Furthermore, the extent of its allergenicity must be provided, including a description of the study populations in which the proposed allergen has been evaluated, routes of exposure, and whether sensitization was defined solely by a case history or additionally by an allergen challenge, serological IgE test, skin test, and/or a cellular test (e.g., basophil histamine release).

Serological assays for IgE antibody use an additional coding system to identify the allergen specificity. They use a unique single letter code for each allergen group followed by a number. The letter codes are: grass pollen (G), weed pollen (W), tree pollen (T), epidermal allergens (E), mold spores and mycelia (M), dust mites (D), insect venoms and excretions (I), foods (F), and occupational allergens (U or K). In addition use of the allergen's common name and scientific name (genus and species) allows further discrimination. For instance, W1 refers to weed 1 which is the code for common ragweed or *Ambrosia artemisiifolia*. Allergenic component nomenclature can be illustrated by F423 that refers to food allergen 423 which is peanut or *Arachis hypogaea* group 2 allergen or Ara h 2.

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Allergens Used In Vivo

For both puncture and intradermal skin tests, allergen in the form of a biological extract is applied to the skin through a scratch, puncture, or interdermal injection, and the skin is observed 15–20 min later for evidence of a wheal and flare reaction. The allergens commonly used are physiological extracts of biological materials. There are different strategies for characterizing clinically used allergen extracts in the United States and Europe (Slater et al. 2012; Kaul et al. 2011; Bartel et al. 2012). In the United States, there are 19 standardized allergen extracts used clinically that have defined amounts of principal allergens and potency assessments. This group includes extracts from dust mites (*Dermatophagoides farinae*, *D. pteronyssinus*), cat hair, cat pelt, short ragweed, Hymenoptera venoms (honeybee, Polistes wasp, yellow jacket, yellow hornet, and white-faced hornet), and the grass pollens from Bermuda, red top, June, perennial rye, orchard, timothy, meadow fescue, and sweet vernal. In the United States, standardized allergenic extracts are compared to reference standards for consistency of potency prior to release by manufacturers. The 1,269 remaining in vivo extracts used clinically are considered by the US Food and Drug Administration (US-FDA) to be nonstandardized which means that they have limited or no potency and stability data. These were grandfathered into clinical use before 1980 when the requirement for demonstrating efficacy was established at the US-FDA. The currently used nonstandardized allergen extracts that are clinically available include the following numbers of each source groups: animal 28, molds 180, dusts 6, plants 16, foods 277, pollens 708, and insects 34.

Reclassification of their status by the FDA has been conducted over many years after careful scrutiny by internal reviewers covering data from 2004 to 2011 and two expert panel reports (21 CFR 601.25 [1974–1979]: 21 CFR 601.26 [1982–1983]). Based on available literature and using decisions about the availability of peer-reviewed evidence demonstrating safety and efficacy, the FDA group subdivided these nonstandardized allergens into five tables (Slater et al. 2012). Table 1 includes 480 extracts in clinical use for diagnosis and treatment with performance that has been reported in peer-reviewed literature. Table 2 includes a list of 134 food extracts that are used in diagnosis. Table 3 lists 73 nonfood extracts that are documented for use in diagnosis only. Table 4 lists 566 problematic allergen extracts that have insufficient literature related to the efficacy in diagnosis or treatment of allergic disease. Table 5 provides a list of 16 extracts that represent potential safety issues such as house dust and monkey pelt. The extracts in Tables 4 and 5 are to be removed from commercial availability due to either concerns about safety or lack of evidence of efficacy (Slater et al. 2012).

The allergens listed in Table 1 of the FDA report are considered to have evidence of safety and efficacy for use in immunotherapy as well as diagnosis. Allergen immunotherapy is designed to treat the cause of the allergic disorder with the goal of improving the patient's quality of life and reducing allergen-induced allergic symptoms. The patient is immunized in the skin, orally or sublingually with increasingly larger doses of allergens to which the individual is allergic. The ultimate goal is to induce immunologic tolerance. Extracts with a known potency and stability or shelf-life need to be used as allergen "vaccines."

Allergens Used In Vitro in Serological Assays

The IgE antibody autoanalyzers used clinically use mostly allergen extract-based reagents to bind IgE from serum. The most comprehensive listing of allergen specificities used in serological assays is presented in Appendix 1 of the Clinical Laboratory Standards Institute's I/LA20 Guidance Document (Matsson et al. 2008). In contrast to the extracts used in vivo for skin testing and immunotherapy, allergen-containing reagents used in serological assays undergo extensive FDA scrutiny in terms of their performance in comparison with a predicate device. In addition, serum samples from individuals known to be clinically allergic to the allergen specificity

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in question are banked and used in inter-batch quality assurance evaluation of reagents. Historically, those allergen specificities that did not have FDA clearance, because there was insufficient performance data with positive IgE antibody-containing sera, were designated as "analyte-specific reagents." Laboratories which provide IgE antibody measurements using ASR-designated allergens are required to perform their own internal validation. Unfortunately, many ASR-related allergen-specific IgE measurements are provided to clinicians who use them to make clinical decisions about patient management when there is less documentation than required for validation. For this reason, the ASR designation is gradually being phased out. Allergen reagents being sold for use in US-FDA cleared autoanalyzers will be required to have performance data submitted to the FDA before they can be used clinically.

The three principal IgE antibody autoanalyzers report different quantitative levels of specific IgE antibody for any given specificity when testing the same sera (Hamilton 2010). This has been attributed at least in part to heterogeneity of allergen-containing reagents (Matsson et al. 2008). Variability can occur even when a single manufacturer uses the same extract source or chemicals and analogous manufacturing procedures. There are a number of cited reasons for interlot and inter-manufacturer heterogeneity. The natural source material for generating a final allergen reagent can be misidentified, contaminated with other allergens, or have a different allergenic composition as a result of natural biological variation. If recombinant allergen sources are used, differences in expression vectors, minor differences in the primary sequence determination, changes in protein folding, and the degree of glycosylation all lead to interlot variability. The extraction process used by different manufacturers which start with the same source material can change the allergen composition of the extract. There can be differences in the coupling or conjugation chemistry since each solid-phase matrix is different. Variability can occur during storage as a result of differential stability of allergen components within an extract. Manufacturers can use different internal allergen reference standards and human serum pools to quality control their final allergen reagent. Finally, each manufacturer has different methods and acceptance criteria that they used to validate their reagents prior to release.

Quality Control of Allergen Reagents

A bank of sera containing IgE antibodies with known specificities are used in a number of immunochemical assays for quality assurance of allergen reagents. These methods include isoelectric focusing combined with immunoblot, Western blot, and competitive inhibition immunoassay analyses. Principal allergens are further characterized following extract preparation by isolation, amino acid sequencing, and cloning of individual allergenic components. Occasionally, the biological activity as determined in a basophil histamine release assay is used to verify the presence of major allergenic components. Ideally, a quality assurance program for allergen-containing reagents documents its identity, relative quantity, and the immunoreactivity of principal allergen components in each of the hundreds of native allergen extracts, allergen isoforms, and recombinant allergens.

A number of tests are used to quality control an initial allergen extract. These include non-immunological methods such as total protein, amino acid measurements, and SDS-polyacrylamide gel electrophoresis (SDS-PAGE) which discriminates native allergenic and nonallergenic components in an extract on the basis of their molecular weight. In addition, isoelectric focusing (IEF) discriminates allergenic components in an extract based on their isoelectric point, and 2D electrophoresis combines the two previous methods discriminating components in an extract or isoforms in a native component preparation by both molecular weight and isoelectric point. Sequencing is used to characterize the primary amino acid sequence and composition of a given allergenic component, and mass spectrometry is applied to native or recombinant allergenic components to document purity and discriminate between isoforms. In addition, immunochemical methods are used

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with characterized human sera such as in an inhibition format of a serological IgE antibody assay and quantitative immunoelectrophoresis.

Component Allergens

Many principal allergens in extract mixtures have been identified, purified, cloned, and sequenced, and their biological properties have been identified. Limited allergen libraries have been established such as food allergen library funded by the EuroPrevall project. In this library, allergenic components from clinically important foods are stored that been validated by extensive physical, chemical, and immunochemical analyses (Hoffmann-Sommergruber and Mills 2009; Alessandri et al. 2012). Allergenic components have also been configured into chip-based multiplex assays that allow rapid simultaneous evaluation of human sera for allergen-component-specific IgE antibodies to multiple allergen specificities (Hiller et al. 2002). The one food specificity where allergenic component-specific IgE has become particularly useful is peanut. Nicolaou et al. (2010) examined a population-based birth cohort with microarray analysis and showed that Ara h 2 is an IgE anti-peanut component specificity that best predicts clinical allergy as evidenced by a failed oral peanut challenge. This observation has been reproduced by others who have shown that Ara h 2-specific IgE antibody when combined with IgE anti-Ara h 1 and 3 can effectively differentiate between peanut allergic and tolerant children (Dang et al. 2012; Ebisawa et al. 2012).

Summary

Allergen is the key component that allows both in vivo and in vitro/serological assays to detect IgE antibody and provide diagnostically useful information. The majority of the diagnostic and therapeutic allergens in use are extracts containing complex protein mixtures that have been prepared as physiological extracts of biological materials. In some cases such as peanut, the individual allergenic components have become useful in identifying sensitized individuals who will manifest severe allergic responses following allergen exposure. The extent of potency assessment, stability and expiration data, and physical chemical validation and quality control varies widely among extracts used in vivo. Federal regulators have more rigid controls on interlot quality control and performance validation of allergenic reagents used for serological detection of IgE antibody in autoanalyzers.

Cross-References

- ▶ Analytes and Biomarkers: IgE
- ▶ Cow's Milk Allergy
- ▶ Diagnostic Assay Components
- ▶ Egg Allergy
- ▶ Food Allergies, Diagnostic Testing
- ▶ Food Allergy, Overview
- ▶ IgE Testing
- ▶ Imported Fire Ant Allergy
- ▶ Peanut Allergy

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Diagnostic Components: T Helper Cell Cytokines (IL-4, IL-5, IL-9, IL-10, IL-13, IL-17)

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Synonyms

ALRH, BHR1, P600; **IL-10:** Human cytokine synthesis inhibitory factor, CSIF; **IL-4:** B cell stimulatory factor-1, BCSF-1; **IL-5:** Colony-stimulatory factor, Eosinophils, CSF-E, Eosinophil differentiation factor, EDF, Terminal differentiation factor, TDF of B cells; **IL-9:** P40, T cell growth factor III **IL-13: IL-17**: CTLA8, IL-17A, IL-17B, IL-17C, IL-17D, IL-17E (IL-25), IL-17F (ML-2)

Definition

The group of proteins known as IL-4, IL-5, IL-13, and IL-10 are commonly referenced as so-called T helper (Th) 2 cytokines that were all originally shown to be products of Th2 cells, as opposed to Th1 cells that generally produce IL-2 and interferon-gamma (IFN-γ) (Bluestone et al. 2009). However, there has long been controversy regarding whether IL-10 should be classified as a Th2 cytokine. For example, IL-10 is located on chromosome 1, whereas IL-4, IL-5, and IL-13 (along with IL-3 and GM-SCF) are all found clustered within chromosome 5 (5q). Moreover, the pleiotropic effects of IL-10 are generally more distant from those associated with IL-4, IL-5, and IL-13. Nonetheless, the grouped classification of these cytokines arose from their overall tendency in possessing anti-inflammatory activity against Th1 cytokine effects. Th17 cytokines represent a fairly recent multimember family of proteins produced by Th17 cells consisting of IL-17A (the first IL-17 family member), IL-17B, IL-17C, IL-17D, IL-17E (also known as IL-25), and IL-17 F (Kawaguchi et al. 2004). IL-9 was originally described as a growth factor for T cells (particularly Th2) and mast cells. The gene for human IL-9 is also on chromosome 5, some 3.2 megabases telomeric from the IL-5/IL-13/IL-4 loci (Jabeen and Kaplan 2012).

Historical Background

As partially indicated by several of the synonyms listed above, IL-4, IL-5, IL-10, and IL-13 were initially described as cytokines that mediated activity on B cells, either in growth and/or in affecting immunoglobulin expression/synthesis. IL-4 was co-discovered independently in 1982 by Maureen Howard while in William Paul's

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laboratory at the National Institutes of Health (NIH) and by Dr. Ellen Vitetta at University of Texas Southwestern (Howard and Paul 1983). As discussed below, it is now known that IL-4 is produced by basophils in addition to Th2 lymphocytes. Other IL-4-producing cells include NKT cells and mouse mast cells. Sources of IL-5 other than Th2 cells include mast cells and eosinophils. IL-13 was discovered by Minty and colleagues in 1993 using a subtracted cDNA library from activated PBMC (Minty et al. 1993). Analyses showed that the gene coding for IL-13 mapped closely to the IL-4 locus on 5q 23–31. IL-13 was initially described as a factor that mediated inhibitory activity on the cytokines produced in response to LPS stimulation of monocytes. In contrast, B cells were reported as one cell type that responded to IL-13, which led to studies showing that it, like IL-4, could induce isotype switching from IgM to IgE (Punnonen et al. 1993). As discussed below, both cytokines are now recognized as key players in allergic disease and in helminth infections. IL-10 was discovered by Vieira and colleagues in 1997 from a tetanus-toxin human T cell clone and showed homology to an open reading frame within the Epstein-Barr virus (BCRFI). IL-10 and BCRFI functioned by inhibiting cytokine synthesis in PBMC. It is now known that IL-10 is produced by many cell types, including monocytes, lymphocytes (particularly so-called T-regulatory cells), B cells, and immature blood dendritic cells.

IL-17A was the first among the IL-17 family to be described, being identified from a rodent T cell hybridoma. As expected, there is a high degree of homology among the family members, with IL-17 F (isoforms 1 and 2, being 55 % and 40 %, respectively) identical to IL-17A. The ranked order of the remaining family members is IL-17B (29 %) > IL-17D (25 %) > IL-17C (23 %) and IL-17E just 17 % of IL-17A (Kolls and Linden 2004).

IL-9 was originally classified as a Th2 cytokine, with many of its functions being attributed to Th2-like activity. However, other classes of T helper cells (such as Th17 and Treg cells) have also been shown to secrete IL-9 under various culture conditions. Support for an independent Th9 phenotype arose from work showing that naive T cells cultured in TGF-β and IL-4 (or Th2 cells cultured with TGF-β alone) differentiated into T cells that stably secrete IL-9 (Jabeen and Kaplan 2012).

Functional Responses

Both IL-4 and IL-13 are capable of playing a critical role in IgE production by inducing isotype switching in B cells from IgM to IgE. Indeed, these two cytokines have in common the ability to mediate similar responses, including the induction of other immune-associated molecules like MHC class II and the low-affinity IgE receptor (CD23). On the contrary, IL-4 plays a critical role in polarizing naive Th0 cells toward the Th2 phenotype, whereas IL-13 seemingly lacks the ability to do so. Instead, IL-13 has been shown to mediate biological activity more consistent with the asthma phenotype, causing airway obstruction by inducing increased airway hyperresponsiveness, goblet cell metaplasia, and mucus hypersecretion (Wynn 2003). Unlike IL-4 and IL-13, IL-5 possesses growth factor-like properties and, in some ways, is more like IL-3 and GM-CSF with regard to function. Indeed, receptors for these three cytokines all share a common β-chain. Most significantly, IL-5 is essential for the development and maturation of eosinophils, which are the most abundant inflammatory cells migrating into allergic lesion sites, including the asthmatic lung. Of the cytokines listed herein, IL-10 is certainly the most pleiotropic in mediating many diverse functional effects on a variety of cell types. Although IL-10 was initially classified as a Th2, its functions make it unlike most cytokines that fall in this category. In fact, IL-10 is best known for its immunoregulatory function and its ability to suppress Th1 cytokine production (e.g., IL-2 and IFN-γ). Unlike IL-4 and IL-13, IL-10 downregulates MHC II expression and thus suppresses antigen-presenting cell (APC) activity. In contrast, IL-10 does have stimulatory function in activating T cells, mast cells, and promoting immunoglobulin synthesis by B cells (Moore et al. 2001).

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The functions mediated by IL-17 cytokines are mostly regulatory in nature and promote diverse inflammatory responses (Kolls and Linden 2004). In particular, IL-17 cytokines act on many other cells types, both immune (e.g., macrophages) and structural (e.g., fibroblasts, endothelial cells, epithelial, keratinocytes), to induce a variety of cytokines (e.g., IL-6, TNF-α, IL-1β), growth factors (e.g., G-CSF, GM-CSF, TGF-β), and chemokines known for inducing neutrophil chemotaxis (e.g., IL-8, GRO-α, MCP-1).

Aside from its original growth function on T cells and mast cells, IL-9 has since been shown to act on several other cell types. In particular, it amplifies IL-4-dependent IgE synthesis from B cells, promotes goblet cell metaplasia, and induces chemokine (e.g., IL-8 and CCL11) production by muscle cells (Jabeen and Kaplan 2012).

Cell Sources

T cell subsets have long been viewed as the primary source of IL-4, IL-5, IL-13, and IL-10. In particular, IL-4, IL-5, and IL-13 are generally referred to as cytokines derived from T helper 2 (Th2) cells, which are often elevated in allergic disease and helminth infections. These conditions are well recognized for possessing a Th2 phenotype (Zhu and Paul 2010). IL-10 is primarily a T cell product as well, but rather than being produced by Th2 cells, it is instead made by T-regulatory cells (Tregs). Two subtypes of Tregs have been described: induced (iTreg) and natural (nTreg). Both develop from $CD4^+$ T cells, either within the thymus (nTreg) or outside (iTreg), and are key IL-10 (and TGF-β)-producing cells that have a key role in inducing peripheral tolerance. Tregs were formally referred to as suppressor T cells (Siri et al. 2012).

Other hematopoietic cells are now known to produce IL-4, IL-5, IL-13, and IL-10. Both IL-4 and IL-13 are produced at relatively high levels by human basophils stimulated through the high-affinity IgE receptor (FcεRI) and to lesser extent when activated by other stimuli (e.g., IL-3) (Schroeder 2011). In fact, recent studies in mice have suggested that basophils represent an important initial source of the IL-4 required for the induction and/or amplification of the Th2 phenotype (Pulendran and Artis 2012). Earlier studies indicated that mast cells and eosinophils also secrete IL-4 but at levels much reduced compared to those secreted by basophils. Instead, several reports have shown that these cells are better at producing IL-5 and IL-13 than they are at making IL-4. With regard to IL-10, many cell types other than T cells are reported to secrete this cytokine, including monocytes, macrophages, and dendritic cells.

IL-17 cytokines were originally reported to be products from a subclass of T cells (e.g., Th17 cells) which are those that are differentiated from $CD4^+$ Th0 cells under the influence of IL-23. Subsequent studies indicate that IL-6 and TGF-β can also differentiate T cells toward the Th17 phenotype. It is probable that IL-17 production is not limited to IL-17 cells. There is some evidence, in fact, that IL-17 F is made by basophils and mast cells (Kawaguchi et al. 2004), and one paper reports IL-17 F (IL-25) being made by eosinophils and basophils (Wang et al. 2007).

As alluded to above, the predominant IL-9-producing cells are T helper cells that have been designated as a new phenotype (i.e., Th9 cells). Some controversy surrounds this designation, given the plasticity of the Th9 phenotype and that Tregs and Th2 cells have been shown to secrete IL-9 under specific conditions. At this time, only mast cells are implicated as a non-T cell source of IL-9 (Jabeen and Kaplan 2012).

Receptors

IL-4 mediates function by binding its receptor, IL-4Rα. However, both IL-4 and IL-13 can induce functional responses by binding the IL-13 receptor, IL-13Rα1, which consists of a heterodimer of IL-4Rα and IL-13Rα1. The binding to IL-13Rα1 by IL-13 is facilitated by the stabilization provided by IL-4Rα.

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Both the IL-4 and IL-13 receptors signal through Janus kinase (JAK)/signal transduction and activator of transcription (STAT) pathways that culminate in STAT6 phosphorylation and activation, which partially accounts for these two cytokines mediating similar functions. A second IL-13 receptor has been described, IL-13Rα2, which binds IL-13, but not IL-4, and does so with high affinity. It has been suggested that this so-called "decoy" receptor may sequester IL-13 and/or act as a negative regulator of IL-13 and IL-4 signaling (Luzina et al. 2012).

Five IL-17 receptors have been identified and are broadly distributed on many immune cells and tissue. IL-17RA is perhaps the best characterized, binding both IL-17A and IL-17 F, and found on endothelial cells, lymphocytes, lung tissue, and fibroblasts. Other receptors include IL-17RB, IL-17RC, IL-17RD, and IL-17 RE, corresponding to each of the cytokine family members (Kawaguchi et al. 2004).

The IL-9 receptor (IL-9R) consists of 2 subunits: the α-chain (IL-9Rα) and a γ-chain common to other cytokine receptors (e.g., IL-2, IL-4, IL-7). IL-9 potentially signals through STAT1, STAT3, and STAT5 pathways. Highest expression of IL-9R is found on Th2 and Th17 cells. Its distribution on non-hematopoietic cells remains unclear at this time (Jabeen and Kaplan 2012).

Role in Clinical Disease

As classic Th2 cytokines, IL-4, IL-5, and IL-13 are all generally elevated in allergic diseases, which is consistent with the fact that IgE, eosinophils, and mucus are also hallmarks in these diseases. Based on the functional attributes mediated by these cytokines, it can be rationalized that IL-4 plays an important role in initiating allergic disease by inducing IgE synthesis from B cells. IL-5 is necessary for the development and maturation of eosinophils, which are the most prevalent immune cells in allergic diseases. Naturally, IL-5 is also elevated in other conditions that do not necessarily have an allergy component but where eosinophil numbers are elevated (e.g., hypereosinophilic syndromes, HES). The functions mediated by IL-13 (e.g., the induction of mucus secretion, airway hyperresponsiveness, and fibrotic lesions) are most consistent with the persistence of allergic inflammation into chronic disease. Allergic individuals often have increased numbers of $CD4^+$ Th2 cells (circulating in blood and in allergic lesions) that secrete these cytokines in vitro, particularly in response to allergens that induce clinically relevant symptoms in the subject.

Although IL-10 was originally described as a Th2 cytokine and was therefore predicted to increase, along with IL-4, IL-5, and IL-13, elevated levels of this immunoregulatory cytokine are not commonly associated with allergic disease, at least in humans. This is consistent with observations made from studies investigating the role of thymic stromal lymphopoietin (TSLP) in promoting the development of Th2 cells (Liu 2009). TSLP-primed DCs acquire the expression of OX-40 ligand (OX-40 L) that, when engaged with OX-40 on naïve T cells (Th0), promotes these cells to develop into so-called inflammatory Th2 cells that produce IL-4, IL-5, IL-13, and TNF-α but no to little IL-10. This is in contrast to conventional/regulatory Th2 cells that produce IL-4, IL-5, IL-13, and IL-10 but little TNF-α. Conclusions arising from this body of work have stressed the belief that regulatory Th2 cells are indeed those that associate with allergic disease, especially since epithelial tissue producing TSLP is a common co-marker.

As noted above, Th2 cells and the IL-4, IL-5, and IL-13 they secrete are also elevated in helminth and other parasitic infections. Indeed, such infections have long been used in mice, as in vivo models for studying Th2-dependent inflammation. As such, these studies show that all three cytokines play a critical role in helping to expel the parasite from the host. They do so by mediating many of the functions described above, such as the formation of IgE antibodies (IL-4/IL-13), inducing eosinophilia (IL-5), and inducing mucus secretion (IL-13). These functional consequences are but a few of many that are instrumental in helping to expel the parasite from the host. Again, the exact role of IL-10 in parasitic infections

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remains unclear, even though its functions suggest a regulatory role. In fact, it has been theorized that elevations of IL-10 in parasitic disease may account, in part, for why allergic disease is not also manifested in these individuals, especially since the immunological phenotype is essentially the same (e.g., increased IgE, IL-4, IL-5, IL-13, Th2 cells, eosinophils, mast cells, and basophils) (Flohr et al. 2009).

The IL-17 family cytokines have been implicated in many diverse disease states, including asthma, rheumatoid arthritis, lupus, allograft rejection, and antitumor immunity. Perhaps the best associations at this time are those between asthma and IL-17 F. As noted above, mast cells and basophils (which themselves are associated with allergic disease) reportedly make this cytokine along with Th17 cells. The airways of asthmatics show IL-17 F expression, which correlates with disease severity. Again, the functions of this cytokine implicate roles in neutrophil chemotaxis and airway remodeling (Kawaguchi et al. 2004).

At this time, the functional activities of IL-9 point to this cytokine having a role in allergic disease and/or in immunity to intestinal parasites. It is therefore not surprising that it mediates Th2-like activity. For example, IL-9 has been shown to augment allergic inflammation in transgenic mouse models. However, it is not an absolute requirement, since its deletion does not prevent the induction of allergic inflammation. IL-9 is also reported to facilitate the expulsion of some parasite, but not to the extent seen with IL-4 and IL-13. Finally, experimental models suggest a role in autoimmune disease (e.g., experimental encephalitis), but evidence for this belief remains limited at this time (Jabeen and Kaplan 2012).

T Helper Cell Transcription Factors

Some of the best evidence to support T helper cell diversity comes from studies identifying the primary transcription factors most associated with subtype development. Briefly mentioned herein for the relevant T helper subtypes discussed above, these include Gata-3 (Th2), RORγt (Th17), FoxP3 (Tregs), and PU.1 (Th9). T-bet is the primary transcription factor in Th1 cells, and Bcl6 has been found in the most recently described T helper cell, so-called T follicular helper (Tfh) T cells. Naturally, there remains considerable overlap with regard to the expression of these so-called master regulators, in that multiple transcription factors can be expressed in any given subtype. However, studies show that deleting the gene coding for an individual transcription factor ablates development of the respective T helper cell subtype.

Therapeutic Targets

In light of their pro-inflammatory nature, many of the cytokines listed above have been targeted for therapeutic intervention. Most often, the approach taken involves making humanized monoclonal antibodies that neutralize soluble cytokines. While the results of clinical trials using anti-IL-4 or anti-IL-5 for reducing the manifestations of allergic disease have been marginal, recent success has been achieved using the latter (e.g., mepolizumab and reslizumab) to markedly reduce eosinophils in conditions such as hypereosinophilia, eosinophilic esophagitis, and nasal polyps. Newer monoclonal antibodies targeting IL-13 cytokine as well as antagonists targeting receptors that prevent IL-4-, IL-5- and IL-13-mediated effects are currently undergoing clinical trials for the treatment of allergic asthma (Catley et al. 2011). Finally, IL-17-specific monoclonal antibodies (e.g., vidofludimus) are being developed for treating psoriasis, inflammatory bowel disease, and rheumatoid arthritis, with recent success reported for psoriasis (Mitra et al. 2013).

Cross-References

- ▶ Basophils
- ▶ Eosinophil Progenitors, Growth, and Differentiation and Death
- ▶ Eosinophilic Esophagitis

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- ▶ Hypereosinophilic Syndromes
- ▶ IgE Isotype Switching
- ▶ IgE-Secreting Plasma Cells
- ▶ Mast Cells
- ▶ Mast Cells, Growth and Development

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Diagnostic Food Challenges

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Synonyms

Oral food challenge

Definition

A food challenge is a diagnostic test involving the ingestion of a food in a supervised medical setting used to diagnose food allergy.

Background

There is a broad range of reactions to orally ingested foods that is collectively called food allergy by the general public. From the perspective of the science of allergy and immunology, food allergy refers to an abnormal immune-mediated reaction after food ingestion. This is in contrast to food intolerances that are nonimmune mediated. These food allergy reactions can be IgE mediated, non-IgE mediated, or mixed. Among the IgE-mediated reactions are the Gell and Coombs type 1 immediate hypersensitivity reactions. These reactions typically occur within 15 min of ingestion, although they can present up to 2 h after ingestion. The symptoms are primarily caused by the release of histamine from mast cells and can range from mild, self-limited

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reactions to life-threatening anaphylaxis. Symptoms can affect the skin, gastrointestinal tract, upper respiratory tract, lower respiratory tract, and cardiovascular system. Examples include urticaria; flushing; eczema; swelling of the face, throat, or extremities; abdominal pain; vomiting; diarrhea; rhinorrhea; sneezing; congestion; coughing; wheezing; shortness of breath; syncope; and shock. Some food reactions that can be both IgE mediated and non-IgE mediated are atopic dermatitis and eosinophilic esophagitis. Examples of non-IgE-mediated food reactions include food-protein-induced enterocolitis syndrome and celiac disease.

The diagnosis of immune-mediated food allergy is primarily dependent on the clinical history. Important historical factors include the type and severity of symptoms, the timing of ingestion in relation to the reaction, the amount of food that is ingested, the heating and preparation of the food, and reactions with any prior ingestions of the food. Unfortunately, meals often include several foods each with a variable numbers of ingredients. Combined with the recall bias of the patient, this can make identification of the causative food difficult. Even when the causative food seems obvious, the nonspecific and subjective nature of some food allergy symptoms can make the diagnosis unclear.

Once the suspicion of food allergy is established by the history, testing to determine the amount of food-specific IgE antibody is commonly used to confirm the diagnosis. This is typically in the form of skin prick testing or in vitro serum assays such as the radioallergosorbent test (RAST) or the newer ImmunoCAP assay (Phadia AB, Uppsala, Sweden). Both skin prick and in vitro testing provide excellent sensitivity (>90 %) but poor specificity (~50 %) (Chapman et al. 2006). As a result, it is not uncommon for testing of broad food allergy panels to result in positive results that may not be clinically relevant. Despite the dependence of many physicians on food-specific IgE testing, decision points based on positive predictive values for the interpretation of these tests have only been established milk, egg, and peanut for skin testing (Hill et al. 2004), and milk, egg, soy, wheat, peanut, and fish for in vitro testing (Sampson 2001). These tests are most appropriate for IgE-mediated food allergy but are sometimes used with variable efficacy for mixed food allergy diseases such as atopic dermatitis to guide food elimination (Caubet and Eigenmann 2010). There is no utility in these tests for non-IgE-mediated food allergy (Sicherer et al. 1998).

A food challenge is a diagnostic tool that involves the oral ingestion of a test food in a supervised medical setting. Although food challenges have been used in the diagnosis of food allergy for many years, there has been significant variability in how the food challenges were actually administered. To address this concern, a 2004 position paper by the European Academy of Allergology and Clinical Immunology (Bindslev-Jensen et al. 2004) and a 2009 American Academy of Allergy, Asthma, and Immunology work group report (Nowak-Wegrzyn et al. 2009) made recommendations to help standardize food challenge administration.

Indications

Food challenges are typically administered to confirm the initial diagnosis of food allergy or to verify that a known food allergy has been outgrown. As an aid in the diagnosis of food allergy, common indications for a food challenge include the following: (1) a strong history but negative skin prick and/or in vitro IgE testing, (2) a strong history but no improvement with elimination, (3) empiric food avoidance based on positive IgE testing or family history without a personal history of reaction, and (4) food allergy reactions that are not readily screened for by available IgE testing such as food-protein-induced enterocolitis syndrome. A food challenge can also be used to guide the reintroduction of foods when multiple foods have been eliminated because of a reaction. Allergies to certain foods such as milk and egg are outgrown by the majority of patients, whereas

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allergies to peanuts and shellfish are rarely outgrown (Wood 2003). Serial IgE testing or a history of tolerating accidental ingestions can suggest that the allergy has been outgrown but a food challenge is often needed to confirm that the allergy has truly been outgrown (Perry et al. 2004).

Risks

Food challenges involve the administration of known allergens. As a result, there is always a risk of an anaphylactic reaction. Reactions to food ingestion typically occur within 15 min of ingestion although they can be present up to 2 h after ingestion. The symptoms are primarily caused by the release of histamine from mast cells and can range from mild, self-limited reactions to life-threatening anaphylaxis. An extensive list of symptoms is included in Table 1 and includes urticaria, throat swelling, abdominal pain and vomiting, coughing and wheezing, lightheadedness, and shock. To address the risk, informed consent is obtained prior to the food challenge and the challenge is only performed by trained medical personnel. In addition, the test site is commonly a medical setting with appropriate resuscitation equipment readily available such as injectable epinephrine, oral antihistamines, inhaled beta-agonists, oxygen, and IV fluids.

Diagnostic Food Challenges, Table 1 Common food allergy reactions

Skin	Urticaria, flushing, eczematous rash, angioedema
Oropharyngeal	Mouth and tongue itch, lip swelling, tongue swelling
Gastrointestinal	Abdominal pain, vomiting, diarrhea, bleeding
Ear, nose, and throat	Rhinorrhea, congestion, sneezing, ear itch, stridor, hoarse voice, throat swelling
Lungs	Cough, wheeze, shortness of breath
Cardiovascular	Palpitations, lightheadedness, syncope, hypotension, shock
Other	Sense of impending doom, fetal position, lethargy

Preparation

The gold standard for the diagnosis of food allergy is a double-blind, placebo-controlled food challenge (Bindslev-Jensen et al. 2004). However, because of the extensive time requirements, increased staff needed to maintain blinding, and the requirement of an appropriate placebo, this is often limited to research settings (Noe et al. 1998). Office-based challenges are most commonly administered without blinding, but occasionally will be single-blind if there is concern for significant patient bias. In most cases, the food in question is already being avoided, but if not, the patient is recommended to remove the food from the diet for 2–4 weeks prior to the challenge. Medications that can alter symptoms during the challenge such as antihistamines and inhaled beta-agonists are stopped at least a week prior as well. Finally, the patient is verified to be in good health on the day of challenge as fever, gastrointestinal illness, and uncontrolled asthma have been shown to increase the risk of severe reaction (Varshney et al. 2009).

Dosing

The cumulative dose of a food challenge is typically 8–10 g of dry food or 100 ml of wet food (Bindslev-Jensen 2001). The food can be taken directly or, in the case of dry foods such as powdered egg white or peanut flour, can be mixed in a carrier food that has previously been tolerated. Table 2 lists common preparations of challenge foods along with typical carrier foods. The test food is administered in several increasing doses with intervals of 10–15 min between doses. Some centers begin with a labial challenge prior to any ingested doses. Although standard protocols are available, the number of doses and interval between doses will occasionally be altered by the pretest probability of a positive reaction and the severity of past reactions. A maximum time for completion of dosing is commonly established to ensure that the effect of the cumulative dose is being measured rather than simply the effect of individual doses. A typical time limit is 90 min. A sample protocol for a cow's milk challenge is shown in Table 3.

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Diagnostic Food Challenges, Table 2 Sample allergen preparations and carrier options

Allergen	Challenge preparations	Sample carrier foods
Cow's Milk	Fresh milk, powdered milk	Soy or hydrolyzed infant formulas, apple sauce, pudding, oatmeal
Egg	Scrambled, hard-boiled, powdered egg white	Apple sauce, pudding, oatmeal
Peanut	Peanut butter, peanut flour	Pudding, oatmeal, yogurt (if not milk allergic)
Soy	Soy milk, soy flour	Infant hydrolyzed formulas, apple sauce, pudding, oatmeal
Wheat	Wheat bread, wheat flour	Apple sauce, pudding, oatmeal

Diagnostic Food Challenges, Table 3 Sample challenge protocol for 100 ml cow's milk

Dose #	Time (min)	Dose amount (% of cumulative dose)	Cumulative dose (cumulative %)
1	0	1 ml (1 %)	1 ml (1 %)
2	15	4 ml (4 %)	5 ml (5 %)
3	30	10 ml (10 %)	15 ml (15 %)
4	45	15 ml (15 %)	30 ml (30 %)
5	60	20 ml (20 %)	50 ml (50 %)
6	75	25 ml (25 %)	75 ml (75 %)
7	90	25 ml (25 %)	100 ml (100 %)

Ending the Challenge

The challenge is discontinued and appropriate treatment is administered if there are objective allergic symptoms. It is also commonly discontinued if there are persistent or worsening subjective allergic symptoms, although this is at the discretion of the administering physician. A list of potential reactions is presented in Table 1. Importantly, it is known that processing can alter the allergenicity of a particular food (Mills et al. 2009). When food challenges are performed with foods in forms that are not commonly ingested, such as egg white flour or peanut flour, negative food challenges are commonly followed by an open feeding of the food in an unaltered form to verify the negative result. The observation time after successful completion of the challenge is typically 1–2 h but can vary depending on the form of food allergy in question, the timing of past reactions, and the severity of past reactions. The suggested observation time after food challenges that result in reactions requiring treatment varies from a minimum of 2 h after antihistamine or beta-agonist treatment to 4 h or more after epinephrine administration.

Interpretation

The terminology used in the reporting of food challenge results can be rather confusing. Despite the negative connotation, a negative food challenge indicates a challenge that is completed with no symptoms. This is also referred to as a passed challenge. A positive food challenge indicates a reaction to the test food resulting in discontinuation of the challenge and is also referred to as a failed challenge. In research settings, the threshold for reaction during a positive food challenge is also occasionally reported. This threshold can be defined as the no observed adverse effect level (NOAEL) represented by the cumulative dose ingested prior to the dose resulting in discontinuation of the challenge. The threshold can also be reported as the lowest observed adverse effect level (LOAEL) or the cumulative dose ingested. Both definitions are complicated by scenarios where subjective symptoms are reported but subside with time and do not result in the discontinuation of the challenge.

After a negative food challenge and an open feeding, the food is immediately reintroduced into the patient's diet. Although the quantity of food should theoretically be unlimited, a conservative approach is to limit ingestion to 1 serving daily for a short period of time prior to introducing it into the diet without limitations. Of note, with respect to peanut allergy, there have been case reports of relapse of the allergic state in those who had previously outgrown the allergy after prolonged periods without peanut ingestion (Fleischer et al. 2004). As a result, at least daily ingestion of peanut is commonly stressed. For positive food challenges, the recommendations are variable and often case dependent. For example, for challenges that result in serious reactions

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or for patients who cannot be trusted to follow guidelines on ingestion, strict avoidance is recommended. In other cases, an arbitrary amount below the LOAEL is recommended as a daily dose to maintain the level of tolerance.

Cross-References

- Cow's Milk Allergy
- Delayed Anaphylaxis to Mammalian Meat (Alpha-gal)
- Egg Allergy
- Epidemiology of Food Allergy
- Food Allergies, Diagnostic Testing
- Food Allergy, Overview
- Food Desensitization
- Methods (In Vivo) Provocation Tests (Nasal Challenge, Bronchial Challenge, Food Challenge)
- Peanut Allergy

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Diagnostic Terms: Atopy

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Synonyms

Atopic march; Atopic syndrome

Definition

Atopy is the genetic predisposition to develop certain allergic hypersensitivity reactions.

Introduction

Atopy is a term that is derived from the Greek word ἀτοπία which is translated as placelessness, out of place, special, unusual, or extraordinary. The term

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was introduced by Coca and Cooke (1923) to refer to individuals who were predisposed to develop certain immediate-type hypersensitivity symptoms following exposure to foreign "allergenic" substances that elicit a specific IgE antibody response. Temporal progression from one atopic disease to another is known as the "atopic march." Typically one may move from atopic dermatitis (eczema) or food allergy in early life to later expression of allergic airways disease such as asthma and allergic rhinitis (Wahn 2009). In select cases, atopic individuals can experience life-threatening allergic reactions such as anaphylaxis following exposure to allergen.

Immunoglobulin E

The gatekeeper of the atopic state is IgE which is one of the five isotypes of human immunoglobulins. It binds onto high-affinity FcεR1 receptors on mast cells, basophils, and dendritic cells which creates a state of sensitization. In the case of dendritic cells, the IgE receptor is utilized to capture allergen for presentation to other immune cells such as T cells. Following allergen reexposure, IgE bound to the surface of mast cells and basophils can become cross-linked, which in turn causes activation of these cells to release various preformed or newly generated chemical mediators such as histamine and leukotriene C4.

In atopic patients, there is a genetic predisposition to produce specific IgE after exposure to allergens. Antigen-presenting cells (APCs) present the degraded protein products of allergens via the major histocompatibility complex (MHC) class II receptors to T-helper 2 (TH2) CD4+ cells. Activated TH2 cells then secrete various cytokines which promote class switching by plasma cells to produce allergen-specific IgE antibodies (Murphy 2011).

Clinical Syndromes

Atopic individuals are more likely to manifest allergic disease(s), most commonly atopic dermatitis, asthma, and allergic rhinitis.

Atopic dermatitis (or eczema) is a chronic inflammatory skin condition. The traditional hypothesis has been that the inflammatory reaction to environmental factors is the primary response to a secondary skin barrier defect (the inside-outside hypothesis). However, recent research has suggested that the primary defect is in the epithelial layer itself. Loss-of-function mutations in the filaggrin gene, which encodes a protein found in the outer epidermis, are associated with atopic dermatitis (Irvine et al. 2011). It most commonly presents in children under the age of 5. Hallmarks of the clinical presentation include pruritus, scratching, and eczematous lesions in characteristic locations. Diagnosis is based on clinical presentation. Treatment includes avoidance of triggers, maintenance and restoration of skin barrier, and anti-inflammatory medications (Leung et al. 2004).

Asthma, like atopic dermatitis, is a chronic inflammatory disease of the airways. It affects 26 million Americans (CDC 2012). A combination of host factors and environmental exposures are thought to be critical factors in the expression of this complex disease. Common clinical symptoms include cough, wheezing, and shortness of breath (EPR3 2007). Treatment includes inhaled corticosteroids, beta-agonists, leukotrienes, and, in severe cases, immunomodulators, such as omalizumab, an anti-IgE monoclonal antibody (EPR3 2007; Stokes and Casale 2009).

Allergic rhinitis is chronic inflammation of the nose due to allergen exposure. It typically is divided into perennial and seasonal etiologies. Common perennial allergens include dust mite, cockroach, animal dander, and mold. Seasonal allergens include trees, grasses, and weed pollens. Symptoms include rhinorrhea, sneezing, postnasal drip, nasal pruritus, and nasal congestion. Diagnosis is based on clinical history and skin test results and/or specific IgE serum levels to suspected allergens. Symptomatic management includes allergen avoidance, nasal corticosteroids, nasal and oral antihistamines, and nasal anticholinergics; a disease-modifying approach includes immunotherapy (Orban et al. 2009).

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Atopic March

The atopic march is the temporal progression that has been observed from atopic dermatitis and food allergy to asthma and allergic rhinitis. Studies have shown that of children with severe atopic dermatitis, more than 50 % will develop asthma and 75 % will develop allergic rhinitis (Spergel 2010). Understanding of the possible contributable factors has been limited. The hygiene hypothesis is the most well known. It proposes that a lack of exposure to certain infectious diseases or decline in certain infections during the first years of life in children from smaller, middle-class families living in industrialized countries may be contributing to the increasing prevalence of atopic diseases (Wahn 2009).

Conclusion

Atopy is the genetic predisposition to produce specific IgE after exposure to allergens. It is associated with three distinct but interconnected diseases: atopic dermatitis, allergic rhinitis, and asthma. The progression from one disease entity to another that is commonly seen in atopic patients is known as the atopic march. Future research may further elucidate the genetic and cellular mechanisms involved.

Cross-References

- Analytes and Biomarkers: IgE
- Asthma Variants: Allergic Asthma
- Atopic Dermatitis
- Diagnostic Terms: Atopy
- Role of IgE in Disease
- Specific IgE

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Diagnostic Terms: Point-of-Care Testing

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Synonyms

Bedside testing; Lateral flow assays; Near-patient testing; POCT

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Definition

Point-of-care testing is a laboratory analysis that is performed outside a central laboratory environment. It is performed nearer to or at the site of the patient, with the results leading to possible change in the compliance and management of the patient.

Introduction

When deciding to move laboratory testing closer to the patient, the question arises whether clinically relevant data that is given to the caregiver at the point of care on a real-time basis can improve the patient's outcome as compared to results generated in a central laboratory using conventional testing methods. Convenience of results that are provided in a timely manner at the point of care may allow more effective clinical examination or counseling by the physician which can eliminate additional visits to the physician's office and avoid the delay of treatment. The availability of more rapid results can allow the physician to more effectively evaluate compliance of a therapeutic regimen with the patient. The type of point-of-care assay needed may differ if the patient is in a hospital clinic versus a physician's office, home setting, or healthcare management company or if the testing is being performed by emergency medical services.

General Considerations

Personnel: The individuals who perform a POCT need basic skills, education, and competency evaluation consistent with the selected assay. They need to be able to collect the proper specimen and for select colorimetric assays, the need to have good visual color discrimination. The quality of the specimen impacts on the quality of the final test result. Some point-of-care tests require color discrimination and thus testing for color blindness should be a part of personnel qualification.

Methodology: The degree of quantification required for effective use of the test result needs to be defined. There are qualitative and semiquantitative assays that do not require instrumentation and which may require only visual interpretation by the assayist. In contrast, quantitative methods often require instrumentation to quantify the concentration of an analyte. There are issues of specimen preparation and manipulation such as centrifugation, filtration, or pipetting that impact on the accuracy of the final result. There are objective and subjective endpoints that may require multiple individuals to read the completed assay to minimize inaccuracies. Quality control needs to be built into the assay to control for variations in the abilities of different personnel and changes in environmental conditions and reagents. There are single-use disposable test cassettes and strips which have a built-in calibrator and multiple-use devices where a two-point calibration is required.

Lateral Flow Assays

The lateral flow assay is possibly the most well-known point-of-care test for both home care and laboratory use. Its most frequently cited example is a hand-held pregnancy assay. It is designed to detect the presence of an analyte in a specimen without the need for specialized equipment. As its alternative name, lateral flow immunochromatographic assay, implies, the assay employs a porous paper or polymer that has the capacity to transport fluid. A sample pad serves as a sponge to hold excess sample which is gradually released onto the paper. The sample fluid (urine or blood) migrates across the paper or polymer through a conjugate pad that contains dried particle-labeled antibody or antigen. The mixture of sample and conjugate continue to migrate along the surface where they interact with an antigen or antibody that has been immobilized on the paper in a fine line. The analyte in the blood binds to the immobilized receptor, and the solubilized-labeled conjugate binds to the bound analyte. A positive result is a colored line that can be visualized by the naked eye.

Using IgE antibody as an illustration (Eigenmann et al. 2009), a drop of blood is added to a cassette that is designed to detect human IgE

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antibody to different allergens. The blood sample fluid migrates through a conjugate pad where it solubilizes dried colloidal gold-conjugated human IgE-specific antibody. The mixture migrates further until it encounters dust mite or other aeroallergens that have been immobilized in separate lines on the paper. The IgE anti-dust mite in the blood sample binds the immobilized dust mite allergen, and it is detected by the gold-labeled antihuman IgE. A positive result is generated as a red line. Lateral flow assays can operate as either a sandwich assay as illustrated with the IgE antibody example or as a competitive binding assay. They can also use colored latex or colloidal gold as labels on the conjugate. Analogous lateral flow assays have been reported to detect IgE antibody to other aeroallergens (Lucassen et al. 2010), food allergens (Sarratud et al. 2010), and Hymenoptera venoms (Pfender et al. 2012).

Summary

Moderately complex assays which are now available in a lateral flow assay configuration allow point-of-care test results to be generated at or near the patient. The consequence is more rapid test results which can positively impact on patient care by improving compliance, facilitating therapeutic decisions, and increasing efficiency by minimizing the need for further visits to the doctor's office.

Cross-References

- ▶ Analytes and Biomarkers: Environmental Allergen Assessment
- ▶ Analytes and Biomarkers: IgE
- ▶ IgE Testing
- ▶ Peanut Allergy
- ▶ Vespid Allergy: Yellow Jackets, Hornets and Wasps

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3-Dimethylaminopropylamine (DMAPA), Allergic Contact Dermatitis to

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Synonyms

Contact dermatitis; Dimethylaminopropylamine

3-Dimethylaminopropylamine (DMAPA) is an aliphatic polyamine which is used as a reagent in the synthesis of surfactants, such as cocamidopropyl betaine. Quite often, it can still be found as a contaminant in these products, presenting a strong sensitizer for delayed-type hypersensitivity immune reactions resulting in eczema. Thus, allergic contact dermatitis caused by soaps, shampoos, and a variety of cosmetics is often due to an allergic reaction against DMAPA.

Cross-References

- ▶ Allergic Contact Dermatitis

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Diseases in DDx of Asthma: Alpha 1 AT Deficiency

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Synonyms

A1AT deficiency; Alpha 1 antitrypsin deficiency

Definition

Alpha 1 antitrypsin deficiency is an inherited disorder that is characterized by early onset emphysema and liver disease.

Background

Alpha 1 antitrypsin (AAT) is a protease inhibitor synthesized primarily in the liver that functions to protect the lung from proteolytic damage (Stoller and Aboussouan 2012). Alpha 1 antitrypsin deficiency is caused by a genetic defect with this protein leading to unopposed neutrophil elastase protease activity in the lung, causing a destructive process leading to emphysema (Kelly et al. 2010). In the liver, the defective AAT protein accumulates in the hepatocytes, leading to clinical liver disease (Stoller and Aboussouan 2012). The gene encoding AAT is on chromosome 14 and is highly polymorphic with over 100 alleles identified (Kelly et al. 2010). Protein variants are codominantly inherited and classified by an alphabetical system based on isoelectric mobility in an electrophoretic field at alkaline pH (ATS/ERS 2003). Various homozygous and heterozygous combinations of deficient or null alleles leading to plasma concentrations of AAT protein below 11 μM are at high risk for developing pulmonary emphysema (Crystal 1998). The normal allele, M, is present in over 95 % of the Caucasian population (ATS/ERS 2003). Homozygosity for the Z allele (PI*ZZ) is associated with very low AAT levels and accounts for virtually all individuals with severe alpha 1 antitrypsin deficiency (Senior and Atkinson 2008). Combining the results of the largest population-based screening studies in the United States suggests the prevalence of PI*ZZ individuals is 1/4,455 (Stoller and Aboussouan 2012).

Clinical Presentation

Most patients with AAT deficiency present with signs and symptoms of chronic obstructive pulmonary disease (COPD) (Stoller and Aboussouan 2012). The emphysema of AAT deficiency tends to be early in onset (fourth and fifth decades), panacinar in pathology, and disproportionately affecting the lung bases (as opposed to apical involvement in AAT-replete COPD patients) (Kelly et al. 2010). Smoking is the most important risk factor for the development of AAT deficiency and can accelerate the development of emphysema in males over age 50 (ATS/ERS 2003).

Homozygous AAT deficiency in infancy is often associated with hepatosplenomegaly, cholestasis, and elevation of hepatocellular enzymes (Shapiro et al. 2010). Liver disease can present with hepatitis, cirrhosis, and hepatoma (Stoller and Aboussouan 2012).

Panniculitis is an uncommon skin condition associated with AAT deficiency that presents with painful, red nodules that can progress to ulceration or necrosis (ATS/ERS 2003). The cause of the panniculitis in AAT deficiency is unopposed proteolysis with subsequent destruction of collagen and elastic fibers in the dermis (Hendrick et al. 1988).

Diagnosis

Targeted testing of AAT deficiency in at-risk groups has been advocated by the American Thoracic Society/European Respiratory Society task force (ATS/ERS 2003). Testing usually begins with

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determining the serum level of AAT (Shapiro et al. 2010). If serum levels are low or when pedigree analysis is needed to clarify familial patters, phenotyping by isoelectric focusing or molecular diagnosis with genotyping is commonly used (Stoller and Aboussouan 2012).

Treatment

Since AAT deficiency is a cause of COPD, the medical treatment and management for COPD also applies to AAT deficiency (Stoller and Aboussouan 2012). Treatment specific to AAT deficiency is centered on augmentation therapy with intravenous infusion of pooled human alpha 1 antitrypsin (Kelly et al. 2010). Clinical trials in the 1980s showed that weekly infusions of alpha 1 antitrypsin increased plasma and lung epithelial fluid AAT to normal levels in AAT-deficient individuals (ATS/ERS 2003). These trials subsequently served as the basis for approval of this product for use in the United States by the Food and Drug Administration in 1988 (Wewers and Crystal 2013).

Cross-References

► Diseases in DDx of Asthma: COPD

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Diseases in DDx of Asthma: Bronchopulmonary Dysplasia

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Synonyms

BPD

Definition

There have been several definitions of bronchopulmonary dysplasia (BPD), use of the term chronic lung disease (CLD) over the years (Ehrenkranz et al. 2005). These terms were used to describe the condition seen in infants who were treated with prolonged mechanical ventilation and high oxygen levels for severe respiratory distress syndrome (Ehrenkranz et al. 2005). Most recently, BPD has been generally defined by National Institutes of Health (NIH) diagnostic criteria as the need for oxygen at 28 days after birth; this can be further defined as to severity, based on the gestational age and amount of supplemental oxygen requirement (Kinsella et al. 2006; Lestrud 2011). This new definition was validated in a study of nearly 5000 infants (Ehrenkranz et al. 2005). In 2006, the bronchopulmonary dysplasia group at the NIH

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further honed this definition to better reflect different endpoints for those born before or after 32 weeks' gestation; this helps to adjust for the more severe neurodevelopmental outcomes in earlier gestational age infants, but there is still a thought that perhaps the definition needs to be more strictly defined even further based on gestational age (Aschner and Walsh 2007). This continues to be a definition in flux.

Etiology and Prevention

Bronchopulmonary dysplasia (BPD) is a disease that is a long-term sequela of prematurity, likely due to a combination of positive-pressure ventilation and treatment with high concentrations of oxygen. It can also occur in term infants who need aggressive ventilator treatment for acute lung disease (Kinsella et al. 2006). As these therapies are used concurrently, it is unclear as to the contributions of each to the ultimate long-term disease (Lazarus 2010). However, use of more modern technologies and treatments has led to a milder, or new, form of BPD, which may be due more to arrest in lung development (Lazarus 2010). BPD can lead to poor growth, due to increased energy expenditures from increased respiratory demands. It can be complicated by gastroesophageal reflux disease, aspiration, and poor growth. Exacerbations in infants with BPD can be triggered by viral respiratory infections, resulting in tachypnea, retractions, wheezing, and an increase in oxygen requirement (Lestrud 2011).

Prevention of the development of BPD is a topic of much research and debate. Use of inhaled nitric oxide has been researched and is challenging due to cost (Jobe 2011). Careful management of oxygen exposure at lower targets compared to term infants could be helpful, as well as use of continuous positive airway response (CPAP) rather than conventional ventilation, to help prevent inflammatory reactions due to oxygen toxicity and barotrauma (Jobe 2011; Kinsella et al. 2006). Prevention by modifying nutrition and enzyme supplementation has also been studied (Kinsella et al. 2006).

Pathology

Pathologic changes seen with original (classic) BPD pathology samples include metaplasia, obliteration, and cystic changes of the bronchioles (Lazarus 2010). Milder (new) BPD pathology, since the advent of the use of surfactant, shows simplified alveolar and alveolar-capillary development, but less commonly any airway abnormalities such as smooth muscle hyperplasia or interstitial fibroproliferation (Lazarus 2010; Hayes et al. 2011).

Treatment and Prognosis

Treatment of established BPD involves normalizing work of breathing. Supplemental oxygen may be required in some infants for varying amounts of time. High caloric intake; treatment of GERD, if present; and monitoring for fluid overload are necessary. β-agonists can help some infants during exacerbations, though may worsen symptoms if airway malacia is present (Lestrud 2011). Infants with more of a classic (old) BPD may have fixed airway obstruction, with little response to β-agonists (Hayes et al. 2011). Patients with frequent inflammation-induced episodes may benefit from inhaled glucocorticoids and leukotriene modifiers. Depending on gestational age, the patient may benefit from immunoprophylaxis for respiratory syncytial virus (RSV) (Lestrud 2011).

The term BPD was chosen over CLD to distinguish this particular presentation from the other chronic lung diseases seen in later life (Ehrendranz et al. 2006). However, infants who have respiratory compromise that is out of proportion compared to their risk of severity of BPD should be evaluated for other pulmonary diseases. These would include asthma, cystic fibrosis, and chronic aspiration. Possible airway abnormalities (stenosis, malacia) should also be evaluated (Lestrud 2011).

Outcomes have changed over the last decades due to several interventions now available for premature infants, as the use of corticosteroids

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antenatally, surfactant, and improved ventilation methods have led to a milder "new" form of BPD. There also may be more infants with BPD, due to improvement in survival rates of very premature infants (Lazarus 2010). However, studies performed in later childhood demonstrate that for children with prematurity of less than 26 weeks or significant airflow obstruction still present at 2 years of age, there is more asthma, more airflow obstruction, and more respiratory symptoms in later childhood (Jobe 2011). Studies of older children and adults who had the classic (old) BPD can have chronic pulmonary function abnormalities, reduced exercise capabilities, and more rapid lung function deterioration compared to normal (Hayes et al. 2011). However, most infants with BPD see a steady improvement in pulmonary function and oxygen requirement, with most off of oxygen by age 2 (Kinsella et al. 2006). Studies have yet to be done on older patients who had mild (new) BPD, due to those patients for whom surfactant was available as a treatment not being old enough to have study outcome; one would assume there could still be some, but perhaps less, impairment of pulmonary function later in childhood and adulthood (Hayes et al. 2011; Kinsella et al. 2006).

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Diseases in DDx of Asthma: COPD

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Synonyms

Chronic obstructive pulmonary disease

Definition

The Global Initiative for Chronic Obstructive Lung Disease defines Chronic Obstructive Lung Disease (COPD) as a common, preventable, and treatable disease, which is characterized by persistent airflow limitation that is usually progressive and associated with an enhanced chronic inflammatory response in the airways and the lung to noxious particles or gases (GOLD 2013). COPD is commonly associated with chronic bronchitis and emphysema. Chronic bronchitis is a clinical diagnosis characterized by chronic cough and sputum production, whereas emphysema is defined anatomically as airspace enlargement due to the disappearance of alveolar space (Wise 2008). Previously COPD was defined in terms of these two conditions, but now it is acknowledged to have a more complex pathogenesis with a need for objective measures of lung function to make the diagnosis (Balkissoon et al. 2011).

Risk Factors

Chronic Obstructive Pulmonary disease results from the complex interaction between genetic

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susceptibility and exposure to environmental stimuli (Decramer et al. 2012). Tobacco smoke is the principle risk factor and environmental toxin responsible for the development of COPD (Martinez and Han 2012). Other environmental exposures include indoor and outdoor air pollution and occupation dusts and chemicals (GOLD 2013). The best documented genetic risk factor for COPD is alpha 1 antitrypsin deficiency, but there are also a number of other candidate genes that might influence disease severity and response to medications (Balkissoon et al. 2011).

History and Exam

Patients will present with dyspnea and cough that may include sputum production. The dyspnea is persistent, progressive, and usually worse with exercise (Shapiro et al. 2010). In severe disease, fatigue, weight loss, and anorexia can also be present (GOLD 2013). Physical examination and chest imaging are insensitive methods for the diagnosis COPD (Wise 2008). Physical signs of airflow obstruction may be present, but usually not until the disease is more severe and significant impairment of lung function has occurred (Shapiro et al. 2010).

Diagnosis

The clinical diagnosis of should be considered in patients with dyspnea, chronic cough, and/or sputum production with a history of exposures to risk factors of the disease (Celli and MacNee 2004). Spirometry should be performed on all patients with suspected COPD with the presence of a post bronchodilator forced expiratory volume in one second (FEV1)/forced vital capacity (FVC) <0.70 confirming persistent airflow limitation that defines the disease (GOLD 2013).

Nonpharmacologic Treatment

Smoking cessation has the greatest influence on the natural history of the disease and prevents the progressive decline in lung function (Wise 2008). Pulmonary rehabilitation, which includes exercise training, nutrition counseling and education, and psychosocial support, has been shown to improve quality of life, decrease hospital stays, and increase exercise capacity (Shapiro et al. 2010). Oxygen therapy increases survival in patients with severe resting hypoxemia and is indicted for patients with PaO_2 below 55 mmHg or SaO_2 below 88 % (GOLD 2013).

Pharmacologic Treatment

Bronchodilators

Short- and long-acting bronchodilators form the cornerstone of management for COPD (Balkissoon et al. 2011). These medications increase FEV1 (forced expiratory volume in one second) or other spirometric factors by relaxing airway smooth muscle tone (Cazzola et al. 2012). Beta agonists, anticholinergics, theophylline, or combination therapy have all been used, and the choice of drug depends on medication availability and individual patient response in terms of symptom relief and side effects (GOLD 2013). Short-acting bronchodilators provide rapid relief of symptoms, but for patients with persistent symptoms requiring daily use of these medications, a switch to long-acting formulations is preferred (Balkissoon et al. 2011). Combining different classes of bronchodilators may be more effective and may decrease side effects as compared to increasing the dose of a single drug (GOLD 2013). Theophylline is less effective than long-acting bronchodilators, and its use is complicated by more side effects and drug interactions (Shapiro et al. 2010). The use of theophylline in COPD is not recommended if long-acting bronchodilators are available and affordable (GOLD 2013).

Corticosteroids

Inhaled corticosteroids reduce the frequency of exacerbations and have also been shown to improve symptoms, quality of life, and lung

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function in patients with an FEV1 of less than 60 % predicted (GOLD 2013). These medications should be added to bronchodilators and not used as monotherapy for COPD (Balkissoon et al. 2011). The use of inhaled corticosteroids is associated with a higher risk of pneumonia among elderly patients with COPD (Ernst et al. 2007). Combining an inhaled corticosteroid with a long-acting beta agonist is more effective than either medication alone in improving lung function, improving health status, and reducing exacerbations in patients with moderate to very severe disease (GOLD 2013). Oral corticosteroids have numerous side effects and should be avoided in the long-term treatment of stable COPD (Shapiro et al. 2010).

Other Pharmacologic Treatments

Roflumilast is an oral daily phosphodietsterase-4 inhibitor that has been shown to improve FEV1 and reduce the risk of exacerbations in patients with severe COPD (O'Byrne and Gauvreau 2009). The use of antibiotics is not recommended except for the treatment of infectious exacerbations and other bacterial infections (GOLD 2013). Both the influenza and pneumococcal vaccines are recommended in patients with COPD (Shapiro et al. 2010). Influenza vaccination can reduce serious illness and mortality in COPD patients, and the pneumococcal vaccine has been shown to reduce community acquired pneumonia in COPD patients under age 65 with an FEV1 less than 40 % predicted (GOLD 2013).

Surgical Treatments

Lung volume reduction surgery has been shown to increase survival compared to medical treatment for patients with severe upper-lobe-predominant emphysema and with low exercise capacity (Naunheim et al. 2006). Current data suggests that in select patients with severe COPD, lung transplantation can improve lung function and quality of life (Christie et al. 2010).

Cross-References

▶ Diseases in DDx of Asthma: Alpha 1 AT Deficiency

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Diseases in DDx of Asthma: Croup

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Synonyms

Laryngotracheitis

Definition

Croup is an upper respiratory infection causing inflammation to the glottic and subglottic areas. Viral respiratory pathogens are the most common causes.

Background

Croup, also known as laryngotracheitis, is the most common form of acute upper respiratory obstruction. Croup is an illness most commonly seen in children under 6, with a peak incidence between 7 and 36 months of age. It is more commonly seen in boys (male:female ratio approximately 1.5:1)(Denny et al. 1983; Cherry 2008).

Natural History

The incidence of croup for all ages is approximately 1.8/100 children in males and 1.3/100 children in females (Denny et al. 1983). Classically, antecedent symptoms include stigmata of a viral upper respiratory tract infection: rhinorrhea, low-grade fever, pharyngitis, and cough. Symptoms typically are mild for several days before an acute worsening in clinical status occurs, often at night. A characteristic "barking" or seal-like cough develops, along with inspiratory stridor, hoarseness, and worsening fever (Yellon et al. 2002). Stridor is amplified by crying and distress (Roosevelt 2011).

Most patients do not progress to increased work of breathing. Hypoxia is uncommon as alveolar gas exchange is not affected. The majority of patients have a self-limited illness that does not require intervention. One study reported that in infants less than or equal to age 2, only 8 % of patients seen in the emergency department required hospital admission (Rosychuk et al. 2010).

Etiology

Parainfluenza virus type 1 is the most common cause of croup. Other viruses associated with croup include rhinovirus, respiratory syncytial virus (RSV), enterovirus, and adenovirus. Occasionally, croup may be caused primarily by a bacterial infection, such as Mycoplasma pneumoniae (Rihkanen et al. 2008). Secondary bacterial infection as a complication of viral croup can also occur, most commonly with Staphylococcus aureus and Streptococcus species (Cherry 2008).

Exam Findings

The status of the patient's airway must be considered first and foremost, as croup is an upper airway disease. Stridor can be either intermittent only with episodes of agitation or present continuously at rest, indicative of more significant obstruction. More severely affected patients can develop retractions of accessory muscles. Coryza, pharyngitis, and hoarseness are commonly appreciated on exam (Roosevelt 2011). Clinical scoring systems exist to help determine severity of croup (Westley et al. 1978).

Radiologic Findings

Radiograph of the neck is not routinely needed. Consideration for imaging should be considered for patients with an atypical clinical course. Only patients with a stable airway should have x-ray performed. The "steeple sign" on posteroanterior

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view can be found, which suggests a reduction in subglottic diameter, although this finding can be a normal variant and does not correlate well with disease severity (Roosevelt 2011).

Treatment

Treatment is based on the severity of croup. Severity is classified into mild, moderate, and severe (Cherry 2008). Mild cases can be managed at home with oral fluids to maintain hydration, breathing either cool or room temperature mist, and antipyretics. Double-blind trials evaluating a single dose of dexamethasone have shown benefit in reducing the rate of return to care and/or duration of symptoms (Geelhoed et al. 1996; Bjornson et al. 2004). Moderate to severe croup is treated with oral corticosteroids, as well as nebulized epinephrine. The length of time spent in the hospital is decreased with corticosteroids (Russell et al. 2011), and symptom severity is improved with racemic epinephrine (Westley et al. 1978).

Cross-References

- ▶ Asthma Variants: Cough-Variant Asthma
- ▶ Diseases in DDx of Asthma: Vocal Cord Dysfunction

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Diseases in DDx of Asthma: Differential Diagnosis of Asthma

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Synonyms

Asthma; Wheezing

Definition

Asthma is a chronic inflammatory state of the airways that causes variable, and reversible, airflow obstruction (Kaplan et al. 2009). It is treatable, but does need to be differentiated from other diagnoses that can mimic asthma, and has different treatment modalities. Specific testing may be required. Wheezing is commonly only present during an exacerbation, and the lack of wheeze during the physical exam does not rule out asthma. Atypical findings in children who wheeze, including symptoms at or soon after birth, failing to thrive, continuous wheezing, or lack of association of wheeze with typical

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triggers (viruses, allergen exposure, exercise), should prompt evaluation for other diagnoses (Liu et al. 2011).

Other Obstructive Lung Diseases

Chronic obstructive pulmonary disease (COPD) is irreversible or partially reversible airflow obstruction, as seen on lung function testing. Patients see a gradual symptom increase over time, compared to defined exacerbations in asthmatics. Exacerbations in COPD are commonly due to infections. This diagnosis can coexist with asthma.

Cystic fibrosis (CF) should be considered in a young child who is not responding to inhaled corticosteroids. The child may seem to be more chronically ill, rather than having episodic viral-induced flares, and have poor weight gain and possibly clubbing or cyanosis of the digits. A sweat test will identify most cases; several states have a screen for CF on their newborn screens which will also help identify most, though not all, cases. Genetic testing for the now numerous identified genetic mutations is available and can be performed by specialists if other testing is not clear.

Immune deficiency should also be considered. These may present as frequent or recurrent pneumonia or bronchitis. Laboratory evaluation should include a complete blood count; quantitative immunoglobulins IgG, IgA, IgM and IgE; and consideration of CH50 and immunologic vaccine responses to screen for immune deficiency. Ciliary dyskinesia results in poor mucus clearance from airways. Ciliary biopsy can identify this. Bronchopulmonary dysplasia (BPD) is a chronic disease which is a sequela of prematurity. BPD is associated with a prolonged oxygen requirement during infancy, from months to years. It may be helped by asthma treatments (inhaled corticosteroids, bronchodilators), though not always.

Infections

Lower respiratory tract infection can present with isolated wheeze and never recur. Viral bronchiolitis, such as from rhinovirus or respiratory syncytial virus (RSV), can cause short-term wheezing during illness. This may be helped or worsened by bronchodilator use. Oxygen, if hypoxemic, and airway suction can be quite helpful as supportive care.

Tuberculosis can be ruled out by placement of a PPD (purified protein derivative) test. Chronic fungal, mycobacterial, or parasitic infections may need to be considered. Parasitic infection could be found with exposure in rural and/or developing countries. Hypersensitivity pneumonitis should be considered in farmers or bird owners or those with certain occupational exposures.

Common Other Considerations

Rhinosinusitis or upper airway cough syndrome can lead to cough caused by postnasal drip. Identification of environmental allergies is helpful, as treating allergic or non-allergic rhinitis, or chronic sinusitis, leads to less postnasal drip and therefore less cough. The patient may have reports of headache or foul breath, though some children do not report obvious symptoms. This may also coexist and complicate asthma control.

Gastroesophageal reflux (GER) may coexist and complicate asthma control, though this is controversial (Boulet 2008). GER may also be present alone and mimic asthma by producing chest pain and/or cough. If present alone, asthma medications would not help reduce the chest pain. GER should be considered if asthma medications are only leading to partial relief of chest pain complaints. GER can be silent (i.e., without chest pain or other obvious symptoms) in children. Upper gastrointestinal series and other GI evaluations can screen for this, but a 24-h pH reflux probe is the gold standard for definitive diagnosis.

Hyperventilation syndrome can be seen with anxiety or panic, and learning biofeedback or treating anxiety may be helpful in reducing or eliminating symptoms. Glottic (vocal cord) dysfunction (VCD) may be evidenced by blunting of the inspiratory loops on spirometry, assuming the patient has appropriate coaching and technique. This can be evaluated by direct flexible rhinolaryngoscopy. Vocal cord retraining

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exercises and specific breathing techniques, particularly for exertion, can help relieve symptoms. VCD can be present alone or coexist with asthma. A habit cough may also mimic cough-variant asthma. The habit cough will typically be present during the day and resolves with sleep.

Mechanical Obstructions Mimicking Asthma

Tracheobronchial tumor or tracheal stenosis can cause nonreversible obstruction/compression of the airways, evidence of which might be seen by spirometry. Chest x-ray can rule out large chest mass.

Congenital malformations such as vascular rings or laryngeal webs cause large airway obstructions. Upper GI may help identify this. Laryngotracheomalacia can present as wheezing and/or increased work of breathing. Bronchoscopy may be needed to evaluate this.

Foreign body aspiration should be thought of with new-onset cough in the absence of other symptoms in a young child; however chronic cough has been known to occur by accidental, and sometimes unrealized, aspiration by adults.

Other Lung Problems Mimicking Asthma

Aspiration should be a consideration. Neurologic abnormalities may predispose children or adults to aspiration due to inadequate cough reflex, thus leaving the airway unprotected during swallowing or reflux. Weakness on exam, or microcephaly, or lack of appropriate gag reflex should raise this concern (Guilbert et al. 2008). Bronchiectasis seen on CT scan suggests CF, ciliary dyskinesia, or immune deficiency. Interstitial lung disease and bronchiolitis obliterans may also need to be considered.

Cardiac

Congenital heart disease in infant may mimic asthma. The infant may be noted to have baseline increased work of breathing, poor weight gain due to energy expenditures from increased respiratory needs, and cyanosis and/or sweating with feeding. Urgent evaluation by a cardiologist should be obtained if any cardiac concern is present.

Congestive heart failure (CHF) is more common in adults but might also occur in children with a known cardiac defect. Overlap symptoms with asthma include cough and breathlessness. On exam there may be ankle edema, jugular venous distension, and weight gain; on history there may be report of nocturnal symptoms within an hour or two after reclining.

Medications

Angiotensin-converting enzyme inhibitors (ACE inhibitor) have in some patients caused cough. Stopping medication leads to improvement in cough.

Other

Sleep disorders such as obstructive sleep apnea could lead to patient report of shortness of breath at night, leading to nighttime awakenings. Overnight sleep study may be helpful in determining the exact cause of the nighttime reports. Obese patients can present with more daytime or nighttime shortness of breath than non-obese patients. A Canadian study found that one-third of obese patients who carried a physician diagnosis of asthma actually had no evidence of asthma once medications were tapered and bronchial challenge performed. The same also occurred in non-obese adults, highlighting the need to use objective measurements for diagnosis (Aaron et al. 2008).

Cross-References

- ▶ Asthma Variants: ABPA
- ▶ Asthma Variants: AERD
- ▶ Asthma Variants: Allergic Asthma
- ▶ Asthma Variants: Cough-Variant Asthma

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- ▶ Diseases in DDx of Asthma: Alpha 1 AT Deficiency
- ▶ Diseases in DDx of Asthma: Bronchopulmonary Dysplasia
- ▶ Diseases in DDx of Asthma: COPD
- ▶ Diseases in DDx of Asthma: Croup
- ▶ Diseases in DDx of Asthma: Differential Diagnosis of Asthma
- ▶ Diseases in DDx of Asthma: Vocal Cord Dysfunction

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Diseases in DDx of Asthma: Vocal Cord Dysfunction

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Synonyms

Paradoxical vocal cord motion; PVCM; VCD

Definition

Vocal cord dysfunction, a common mimicker of asthma, is characterized by a transient obstruction of the upper airway associated with the paradoxical adduction or closure of the vocal folds.

Vocal cord dysfunction (VCD), also known as paradoxical vocal cord motion (PVCM), is a transient obstruction of the upper airway associated with the paradoxical adduction or closure of the vocal folds. Although it occurs primarily during inhalation, VCD can occur during either or both stages of the respiratory cycle (Newman and Dubester 1994; Perkner et al. 1998; McFadden and Zawadski 1996; Reisner and Nelson 1997; Newman et al. 1995).

Clinical Presentation

The clinical presentation of VCD ranges from no symptoms to mild dyspnea to acute respiratory distress, which can be mistaken for an asthma attack (Maillard et al. 2000). Patients typically complain of acute onset difficulty breathing, tightness localized to the throat region, and in some cases stridor and/or laryngeal wheezing (Newman et al. 1995; Andianopoulos et al. 2000; Mathers-Schmidt 2001). Dyspneic events may be described as air hunger or a sensation of choking and can be quite frightening, eliciting panic and anxiety in some patients, a response which unfortunately tends to perpetuate the dysfunctional vocal cord movement and worsen the respiratory symptoms. Additional symptoms, which are variable among patients, can include chest tightness or pain, difficulty swallowing, a globus pharyngeus sensation, intermittent aphonia or dysphonia, neck or chest retractions, fatigue, or throat clearing during episodes. Notably, the majority of patients have a concomitant chronic cough (Newman et al. 1995; Andianopoulos et al. 2000; Diamond et al. 2000).

VCD episodes frequently begin and end abruptly (Vlahakis et al. 2002), and specific triggers can only sometimes be identified. Self-reported triggers may include one or several of the following: upper respiratory infections,

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occupational exposures, talking, laughing, singing, acid reflux, cough, foods, physical exertion, exercise, postnasal drip, weather changes, emotional stressors, odors, strong scents, and other airborne irritants (Andianopoulos et al. 2000; Morrison et al. 1999). Some patients have been shown to demonstrate a priming effect, whereby they transition from having a single trigger to gradually being triggered by multiple, previously benign, agents. If VCD is triggered in a large group setting, it can set off a mass hysteria-like reaction, sometimes due to an identifiable noxious exposure (Jones et al. 2000; Cairns-Pastor 2003) but sometimes due to a contagious hysteria with no obvious trigger (Christopher and Morris 2010; Arndt and Voth 1996).

Epidemiology

Once thought to be a psychiatric disorder of women between 20 and 40 years of age, particularly those with a medical background and victims of prior abuse (Christopher et al. 1983), VCD is now thought to affect a much broader patient base. A literature review by Brugman et al. of 1530 patients with VCD found that 65 % of these patients were adults, classified as older than 19 years of age, but that the remainder were actually children and adolescents. The age range of these patients was very broad, ranging from 0.02 to 82 years of age, with a median age of 36.5 years for the adults in the group and 14 years for the pediatric patients. For all age groups, there was a 3:1 female predominance (Brugman 2003).

Although some authors have attempted to capture the prevalence of VCD through literature review and retrospective study (Brugman 2003; Morris et al. 2006; Patterson and O'Connell 1994), its true incidence remains unknown and is thought to fall somewhere between 2 % in patients presenting with an asthma exacerbation or dyspnea as their chief complaint to a percentage as high as 27 % in another study looking at non-asthmatic teens and young adults (Kenn et al. 1997; Mathers-Schmidt 2001). Two separate studies looking at adults and children with refractory asthma found that 40 % and 14 %, respectively, had a diagnosis of VCD, either as their primary diagnosis or as a comorbidity of their asthma (Newman and Dubester 1994; Gavin et al. 1998). Overall, VCD is a diagnosis that is likely underappreciated in clinical practice, and a large prospective study of the general population would be necessary to establish its true incidence.

Diagnostic Approach

The comprehensive approach to patients with possible VCD is summarized in Box 1 below.

A careful clinical history may provide valuable information in diagnosing VCD (Brugman 2007; Martin et al. 1987). A targeted line of questioning around pertinent features of VCD, such as specific signs, symptoms, and predisposing factors, may help distinguish VCD from other respiratory conditions, including asthma and other disorders known to cause upper airway obstruction (Brugman 2007). These features are summarized in Box 2 below.

Many of the signs and symptoms listed in Box 2 can help direct suspicion toward the upper airway as the area of the dysfunction, and patients will often point to or grab their throat when describing their respiratory symptoms (Altman et al. 2002; Martin et al. 1987). Hyperventilation is quite common among patients with VCD, leading to symptoms of light-headedness, visual changes, numbness, or tingling in 76 % of VCD patients in a study by Parker and Berg (2002).

Direct visualization of the vocal folds via flexible, transnasal fiberoptic laryngoscopy during an acute attack remains the gold standard for diagnosis of VCD (Perkner et al. 1998; Newman et al. 1995; Morris et al. 2006; Patterson and O'Connell 1994; Brugman 2007). The characteristic finding of VCD during laryngoscopy is of paradoxical adduction of the vocal cords on inspiration, as shown in Fig. 1.

Unlike the respiratory symptoms caused by an acute asthma attack, VCD attacks do not usually impede panting, speaking, or taking

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deep breaths (Brugman 2007). Hence, patients should be instructed to perform various maneuvers during laryngoscopy, including sequential phonation, normal breathing, panting, and repetitive deep breaths, in order to assess vocal cord movement in a comprehensive manner (Newman and Dubester 1994; Morris et al. 2006). Newman and colleagues reported findings diagnostic of VCD in 100 % of patients undergoing laryngoscopy while symptomatic and in 60 % of patients that were asymptomatic at the time of evaluation (Newman et al. 1995). In order to trigger the symptoms of VCD for diagnostic purposes, one can use a methacholine challenge, immediately followed by flexible laryngoscopy. If methacholine challenge fails to elicit VCD in patients with a compelling history, a specific challenge to a known irritant, ideally performed in a challenge chamber under close observation, may be indicated (Balkissoon 2002; Stanton and Bucknall 2005). Provocation with exercise is required to elicit symptoms in those patients with exercise-induced VCD (Newman and Dubester 1994; McFadden and Zawadski 1996; Morris et al. 1999).

Spirometry can be helpful in suspecting a diagnosis of VCD. A characteristic finding of nonorganic extrathoracic airway obstruction is a highly variable, non-reproducible, and abnormal configuration of the inspiratory loop during spirometry, as shown in Fig. 2 (Brugman 2007; Balkissoon 2002).

Flattening or truncation of the inspiratory flow loop and irregularities such a saw-toothed pattern can be observed during an acute VCD attack (Newman and Dubester 1994; Altman et al. 2002; Balkissoon 2002) but also when patients are asymptomatic (Newman et al. 1995). Because similar abnormalities can also be seen in other laryngeal disorders, clinical context becomes crucial in differentiating disorders of the larynx (Altman et al. 2002). Importantly, organic causes of upper airway obstruction will often serve as a fixed obstruction and yield blunting of both the inspiratory and expiratory loops, which should prompt a radiologic and endoscopic evaluation looking for a fixed obstructive process rather than for a functional disorder like VCD (Newman and Dubester 1994).

BOX 1 Approach to the Patient with Possible VCD

1. **Clinical history and physical examination**
   - Questions regarding symptoms
     - Do you have more trouble getting air in or getting air out?
     - Do you feel any tightness?
     - If so, where is the tightness located? (throat, upper chest, lower chest)
     - Do you hear any noises when you breathe in?
     - When symptoms start, do you generally cough?
     - Do you ever lose your voice or have a change in the way your voice sounds?
     - Do you have numbness or tingling in your hands, feet, or lips during episodes?
     - Do you ever feel lightheaded or dizzy?
     - Have you ever passed out or felt as though you were going to pass out?
     - Do symptoms come on rapidly?
     - Do symptoms resolve rapidly?
     - Do asthma medications help?
     - Does use of your asthma inhalers sometimes make symptoms worse?
   - Assessing for potential risk factors or laryngopharyngeal irritants
     - Gastroesophageal reflux disease (GERD)/laryngopharyngeal reflux (LPR)
     - Postnasal drip due to upper airway inflammatory conditions
     - Psychological factors
     - Other risk factors listed in Box 2
   - Physical examination
     - Rule out upper airway obstruction from an organic cause.
     - Look for signs of upper airway inflammation or allergic rhinitis.
     - Look for signs of acute VCD: stridor, tachypnea, hoarseness or

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dysphonia, cough, tugging of the neck or upper chest muscles, and a look of anxiety or even distress.
- Response to treatment
  - During acute episode, no improvement or even worsening with inhaled medications
  - During chronic management, lack of response to escalating asthma therapy including corticosteroids

2. **Pulmonary function testing**
   - Inspiratory flow loop that is often poorly reproducible and truncated, saw-toothed, or irregular.
   - $FEF_{50}/FIF_{50} > 1$.
   - If FEV_1 is reduced, forced expiratory volume in one second (FEV_1)/forced vital capacity (FVC) ratio will be normal.
   - Normal lung volumes.
3. **Measure of oxygenation and ventilation during episodes**
   - Pulse oximetry normal
   - Normal oxygen tension measured on arterial blood gas (P_aO_2)
   - Normal Alveolar-arterial (A-a) gradient
   - Reduced arterial PCO_2 due to hyperventilation
4. **Flexible Laryngoscopy**
   - Paradoxical adduction of vocal cords during inhalation
   - Posterior chinking
   - Inappropriate adduction of vocal cords during exhalation
   - Secondary evidence of postnasal drip/GERD/LPR (edema and erythema of the glottic and/or periglottic region)

BOX 2 Important Aspects of the Clinical History in a VCD Patient

1. **Symptoms of VCD**
   - Throat or upper chest tightness
   - Shortness of breath or dyspnea
   - Sensation of choking or suffocation
   - More difficulty getting air "in" than "out"
   - Cough
   - Light-headedness or dizziness
   - Heavy sensation of the extremities
   - Perioral or extremity numbness or tingling
   - Rapid onset and rapid resolution of these symptoms
2. **Signs of VCD**
   - Tachypnea or hyperventilation
   - Stridor
   - Neck or chest retractions
   - Pallor but no cyanosis
   - Hoarseness or dysphonia
   - Lack of relief, and sometimes worsening, from asthma inhalers
3. **Risk factors for VCD**
   - Upper airway inflammation (allergic or nonallergic rhinitis, chronic sinusitis, recurrent upper respiratory infections)
   - Gastroesophageal reflux disease
   - Prior traumatic event involving breathing (e.g., suffocation, near drowning, witnessing a severe asthma attack)
   - Severe emotional distress
   - Female gender
   - Playing a wind instrument
   - Competitive athletics

Management

Speech therapy, which consists of a detailed assessment followed by comprehensive treatment, is regarded as the primary treatment for VCD (Newman and Dubester 1994; Brugman 2007; Newman et al. 1995; Vlahakis et al. 2002; Patterson and O'Connell 1994; Lacy and McManis 1994; Goldman and Muers 1991). Speech therapists, also known as vocal pathologists, play an important role in long-term management of VCD by providing assessment and diagnostic input as well as the following therapeutic interventions:

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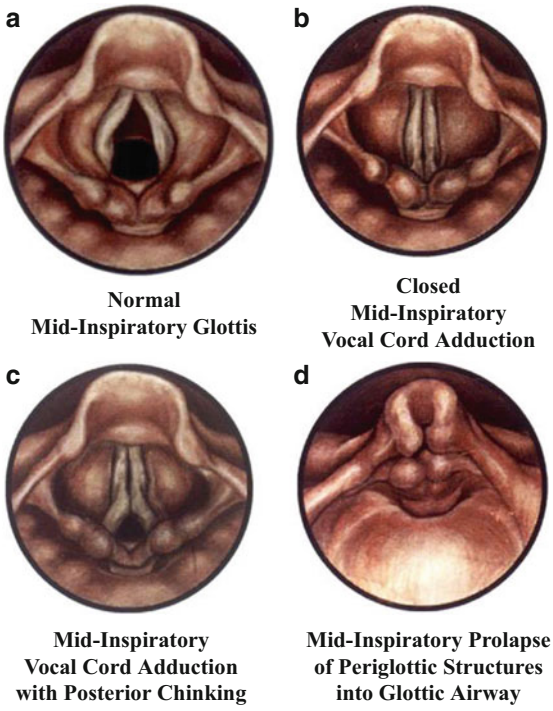
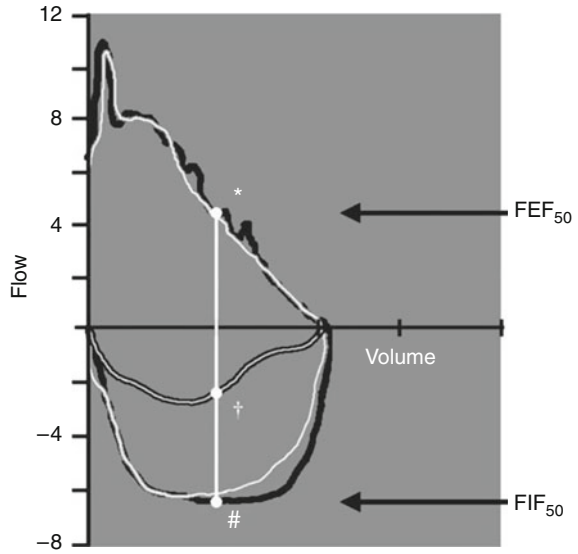


Diseases in DDx of Asthma: Vocal Cord Dysfunction, Fig. 1 Vocal cord movement in patients with and without functional upper airway obstruction. (**a**) Normal vocal cord appearance at mid-inspiration; (**b**) paradoxical adduction of the vocal cords during mid-inspiration, as seen in most cases of VCD; (**c**) partial adduction of the vocal cords with posterior chinking, as seen in a small percentage of VCD cases; (**d**) prolapse of the periglottic structures, as seen in intermittent arytenoid region prolapse (IARP), also known as functional laryngomalacia (Borrowed, with permission, from Hicks et al. (2008))



Diseases in DDx of Asthma: Vocal Cord Dysfunction, Fig. 2 Flow-volume loop showing normal inspiratory loop (deeper loop, marked with #) and the truncated inspiratory loop of VCD (flattened loop, marked with †). The forced expiratory flow at 50 % of the vital capacity (FEF_{50}) is marked with *. The forced inspiratory flow at 50 % of the vital capacity (FIF_{50}) is marked with # on the normal inspiratory loop and with † on the VCD inspiratory loop. The FEF_{50}/FIF_{50} ratio is normally less than 1, as demonstrated by the ratio of * to #. In VCD, the FEF_{50}/FIF_{50} ratio is usually greater than one, as shown by the ratio of * to † (Borrowed, with permission, from Hicks et al. (2008))

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patient education, supportive counseling, management/suppression of laryngeal abusive behaviors (i.e., cough and throat clearing), voice therapy, respiratory retraining, and desensitization to specific irritants (Mathers-Schmidt 2001; Vlahakis et al. 2002; Balkissoon 2002).

Quick-release techniques are the main tool used by speech therapists for the management of VCD and can be used either for prevention of VCD attacks or control of symptoms once these attacks begin. To maximize the benefit of these techniques, patients are encouraged to recognize triggers for their episodes, so that they might use a given technique as soon as they realize they have been exposed to a known trigger, instead of waiting for the onset of symptoms. Quick-release techniques are also used for desensitization to specific irritants and to prevent and/or control VCD attacks brought on by exercise. With the help of a specific irritant challenge, patients whose VCD attacks are brought on by irritant exposures can undergo progressive desensitization such that they can eventually control and eventually prevent episodes. Exercise challenges can be used in a similar fashion for patients with exercise-induced VCD.

In addition to speech therapy for control of the vocal cords, management of VCD also includes removal of triggers. Patients with psychological triggers, for example, will often benefit from psychological counseling (Morris 2006). For patients with physical triggers, the most common of which are gastroesophageal reflux (GERD) and upper airway drainage, therapy involves treatment of these conditions to minimize vocal cord inflammation with resultant hyperreactivity and VCD.

Cross-References

▶ Diseases in DDx of Asthma: Differential Diagnosis of Asthma

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Diseases in Differential Diagnosis of Asthma: Hypersensitivity Pneumonitis

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Synonyms

Extrinsic allergic alveolitis

Definition

Hypersensitivity pneumonitis (HP), also known as extrinsic allergic alveolitis (EAA), is a complicated syndrome of pulmonary inflammation that occurs in response to a wide variety of inhaled agents, including biologic dusts, chemical agents, medications, and microorganisms. The disease can involve the alveoli but also the interstitium and middle and terminal airways. The immunologic mechanism is likely due to activation of T-helper cell type 1 (Th1) lymphocytes in response to inhaled environmental antigens, as opposed to T-helper cell type 2 (Th2) or immunoglobulin E responses (Fink and Zacharisen 2003).

Epidemiology

The prevalence and incidence of HP are not well known; few epidemiologic studies have been performed, and the complexity of the syndrome has made a consensus on diagnostic criteria difficult. One of the most common forms of HP, farmer's lung, has a reported prevalence ranging from 2 % to 9 % (Dalphi et al. 1993; Grant et al. 1972). Incidence has a similar degree of variability. Several factors appear to be at work here, including level of antigen exposure, climate, and local agricultural, and industry practices (Lopez and Salvaggio 1987). Host risk factors are also important; interestingly, HP is less common in cigarette smokers than nonsmokers (Cormier et al. 1988).

Causes

There is an extensive and diverse array of antigens that have been reported as causing HP. Broadly speaking, the categories of potential causes include microorganisms, animal products, plant products, reactive chemicals, and medications. These antigens typically cause sensitization when particles 5 μm or smaller are inhaled, allowing delivery to the alveoli (Nakagawa-Yoshida et al. 1997). A list of some representative antigens is listed in Table 1, but over 300 causative antigens have been identified (Selman 2003).

Classification

The tremendous variability of HP has resulted in four different classification systems. Under the classical scheme, HP is defined as acute, subacute, or chronic (Richerson et al. 1989). In 1982, Boyd et al. published HP categories of acute progressive, acute intermittent nonprogressive,

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Diseases in Differential Diagnosis of Asthma: Hypersensitivity Pneumonitis, Table 1 Causative antigens in HP

Antigen	Examples	Sources	Diseases
Bacteria	Thermophilic actinomycetes, Mycobacteria, Pseudomonas, Bacillus	Moldy hay, compost, dust, hot tubs	Farmer's lung, ventilation pneumonitis
Fungi	Aspergillus, Alternaria, Penicillium, Epicoccum	Moldy hay, water, compost, dust	Compost lung, woodworker's lung
Animal protein	Avian, mammal proteins, cats, animal furs, rodent urine, oyster shells	Pigeon, parrot, pituitary snuff, cat hair, furs, laboratory animal urine, shell dust	Bird fancier's lung, furrier's lung, laboratory worker's lung, oyster shell lung
Insect protein	Sitophilus granarius, silkworm larvae	Infested wheat flour	Miller's disease
Amoebae	Naegleria gruberi, Acanthamoeba castellanii	Contaminated ventilation	Ventilation pneumonitis
Chemicals	Diisocyanates, anhydrides, pyrethrum	Varnishes, resin, adhesive, plastic	Paint refinisher's lung, chemical worker's lung
Drugs/ reagents	Amiodarone, clozapine, cyclosporine, Pauli's reagent	Medications, lab reagents	Drug-induced HP, Pauli's HP
Plants	Soybean hull, tobacco leaves, coffee/tea dust, wood/saw dust	Animal feed, tobacco dust	Tobacco grower's lung, woodworker's lung

Adapted from Fink and Zacharisen (2003).

or nonacute. Cormier and Lacasse in 1996 simply delineated HP as being acute or residual. Finally, in the Selman classification system, HP is distinguished into four distinct definitions: active nonprogressive and intermittent, active progressive and intermittent, chronic nonprogressive, and chronic progressive (Schwartz and King 2011).

Clinical Manifestations

The clinical presentation and course of HP is not consistent; instead, it depends on three main features. These include the specific inhaled antigen itself, the nature of the antigen exposure (i.e., frequency and intensity), and the resultant immune response in the patient. If a patient suffers other simultaneous damage to the lungs (e.g., respiratory infection), this may also influence the disease (Dakhama et al. 1999).

In the acute presentation of HP, which typically occurs 4–6 h after exposure to an antigen to which a patient has become sensitized, there are severe systemic and respiratory symptoms such as fever, chills, myalgias, malaise, nausea, cough, dyspnea, and chest tightness. On examination, patients may exhibit tachypnea and diffuse end-inspiratory rales. Recovery usually occurs spontaneously within hours to days of cessation of antigen exposure (Fink and Zacharisen 2003).

With subacute presentations, there may be progressive respiratory and systemic symptoms such as dyspnea, productive cough, malaise, and anorexia; the more pronounced systemic symptoms of acute HP, such as fever, are usually absent, although respiratory symptoms are worse. Recovery occurs more slowly (Fink and Zacharisen 2003).

Chronic HP may result after longer durations of antigen exposure. Irreversible pulmonary damage is common. Symptoms include progressive dyspnea, cough, fatigue, and weight loss (Pepys 1969).

Diagnosis

Diagnosis of HP is based upon a combination of history and physical examination, laboratory and radiographic findings, physiological testing, and response to removal and/or reintroduction of a suspected problematic antigen (Table 2).

The differential diagnosis of HP is very broad and includes many diseases, such as chronic infections, chronic bronchitis, asthma, airway-centered interstitial fibrosis, connective tissue diseases, sarcoidosis, organic dust toxic syndrome (ODTS), and malignancy (Fink and Zacharisen 2003).

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Diseases in Differential Diagnosis of Asthma: Hypersensitivity Pneumonitis, Table 2 Proposed diagnostic criteria for HP

1. Known exposure to offending antigens	A. History of exposure
	B. Confirmation of antigen in environment
	C. Positive serum precipitins against the antigen
2. Compatible clinical, radiographic, or physiologic presentation	A. Suggestive respiratory/constitutional symptoms/signs
	B. Chest radiograph or high-resolution CT chest (HRCT) with reticular, nodular, or ground-glass opacity
	C. Worsened spirometry, DLCO, or gas exchange
3. BAL with lymphocytosis	A. Low CD4:CD8 ratio is typical
	B. Positive lymphocyte transformation assay to etiologic antigen
4. Positive inhalation challenge testing	A. Environmental reexposure
	B. Inhalation challenge
5. Compatible histopathology (one of the following)	A. Granulomas (noncaseating and poorly formed)
	B. Infiltrate of mononuclear cells

King (2013)

Treatment

Most HP patients will have total resolution of symptoms and pulmonary function impairment within days to weeks after antigen exposure has discontinued. Therefore, elimination of antigen exposure is by far the most critical component of management. This may require removal of the antigen from the home or workplace, use of protective equipment, cessation of certain activities, or discontinuation of offending medications.

In subacute or chronic HP, patients may continue to have progressive disease despite antigen exposure cessation. In these cases, glucocorticoid treatment with 0.5–1 mg of prednisone per kilogram of ideal body weight per day (up to 60 mg/day) may be indicated. After 1–2 weeks, this dose is often then tapered over 2–4 weeks. In rare cases, maintenance treatment is necessary. However, while steroids led to more rapid symptom resolution in one study of 93 farmer's lung patients, no long-term difference was seen (Mönkäre 1983).

Prognosis

Again, most cases of HP result in almost complete symptomatic and pulmonary function recovery. However, this may take years after antigen exposure is discontinued. Pulmonary fibrosis is a poor prognostic indicator. HP is a very heterogeneous syndrome, and so recovery is also dependent on specific etiologic antigen exposure; disease due to avian exposure (bird fancier's lung) seems to portend a worse prognosis than farmer's lung (King 2013).

Cross-References

- ▶ Asthma Variants: Allergic Asthma
- ▶ Testing: High-Resolution Chest Computed Tomography Scan

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E

Egg Allergy

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Synonyms

Egg protein allergy; IgE-mediated food allergy to egg; IgE-mediated food sensitivity to egg

Definition

Egg allergy most commonly refers to an IgE-mediated reaction upon ingestion of egg protein, but it can also refer to other allergic syndromes such as atopic dermatitis and eosinophilic esophagitis (Hill et al. 2008). Egg allergy is the second most common food allergy in young children and infants (Sicherer and Sampson 2006). IgE-mediated reactions are rapid in onset (usually within minutes to 2 h after ingestion), and symptoms such as urticaria, angioedema, respiratory symptoms, gastrointestinal symptoms, and laryngeal edema are common. The severity of symptoms can range from mild to life-threatening anaphylaxis. The proteins in hen's egg that have been implicated in the IgE-mediated response are named Gal d 1–5 (Heine et al. 2006). Most of these proteins are found within the egg white. Ovomucoid (Gal d 1) has been found to be the dominant allergen in hen's egg, while ovalbumin (Gal d 2) is the most abundant. Recent studies have found that the majority of IgE-mediated egg-allergic individuals can tolerate extensively heated egg (Lemon-Mulé et al. 2008). These differing phenotypes are thought to be secondary to certain individuals having egg-specific IgE that is targeted to either sequential or conformational epitopes on the egg protein. Since conformational epitopes (which contain amino acids in proximity secondary to folding of the protein) can be degraded with heat, those egg-allergic individuals that have egg-specific IgE directed at these "targets" can tolerate extensively heated egg. This is not the case for those affected individuals with egg-specific IgE directed at sequential epitopes (with contiguous amino acids) that are not degraded with extensive heating.

Cross-References

- ▶ Atopic Dermatitis
- ▶ Epidemiology of Food Allergy
- ▶ Peanut Allergy

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Emergent Allergies in Cosmetics

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Synonyms/Acronyms

1,3-Butylene glycol (1,3-BG); Allergic contact dermatitis (ACD); Allergy to cosmetics: strange allergens; Cocamidopropyl betaine (CAPB); Dicaprylyl maleate (DCM); Dimethylol dimethyl (DMDM); Food and Drug Administration (FDA); Food colors certified and allowed by the USA for the Food, Pharmaceutical, Cosmetics, and Personal Care industry (FD&C); Hydrolyzed wheat protein (HWP); Iodopropynyl butylcarbamate (IPBC); Isopalmityl diglyceryl sebacate (DGS); Methoxypolyethylene glycol (PEG); Para-aminobenzoic acid (PABA); Pentaerythritol rosinate (PER); Pentylene glycol (PTG); Petrolatum (pet.); Polyethylene glycol (PEG); Polyvinylpyrrolidone (PVP); p-Phenylenediamine (PPD); Propylene glycol (PG); Remarkable allergens in cosmetics; Unusual allergens in cosmetics

Definition

Emerging allergens in cosmetics are those new or unusual allergens identified among the cosmetic compounds that can have broad clinical relevance in the population that uses them and potentially may impact the patients most likely to be sensitive to a cosmetic.

Introduction

The Federal Food, Drug, and Cosmetic Act (FD&C Act) defines cosmetics by their intended use as "articles intended to be rubbed, poured, sprinkled, or sprayed on, introduced into, or otherwise applied to the human body. . .for cleansing, beautifying, promoting attractiveness, or altering the appearance" [FD&C Act, Sec. 201(i)]. Among the products included in this definition are skin moisturizers, perfumes, lipsticks, fingernail polishes, eye and facial makeup preparations, cleansing shampoos, permanent waves, hair colors, and deodorants, as well as any substance intended for use as a component of a cosmetic product.

The term cosmetics has a broad definition and includes personal care products, hair care products, nail care products, and sunscreen (Alani et al. 2013).

The most common allergens in cosmetics are fragrances and preservatives. Suspected diagnosis of cosmetic allergy is made by reviewing the patient clinical history and physical examination findings; the diagnosis will be confirmed with skin patch testing. Standard patch testing is the method allergens responsible for eliciting a cosmetic contact dermatitis (Patel and Belsito 2012).

New cosmetic products continue to be released, and the variety of individual ingredients used to make them continues to change.

The contact allergens can be found in standard batteries recommended by different research groups for contact dermatitis. Contact allergy surveillance groups are organizations that monitor and evaluate contact sensitization based on clinical data collected by participating dermatology departments. These groups aim to protect the population from contact allergens by detecting trends and monitoring frequency of contact sensitization, evaluating the effectiveness of intervention (government legislation) and improving standardization of the patch test procedure on an international level (Alani et al. 2013).

It has been stated that the contact allergy prevalence in consecutively tested patients should

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Emergent Allergies in Cosmetics, Table 1 Emergent allergens in cosmetics

Allergen group	Allergen subgroup	Emergent allergen
Fragrances		***Limonene***
Preservatives	Antimicrobials	**Iodopropynyl butylcarbamate**
	Antioxidants	**Idebenone**
	UV light absorbers	**Octocrylene**
Natural botanicals		**HWP, oat/soybean extract**
		Propolis
Vehicles	Glycols	**1,3-Butylene glycol**
	Alkyl glucosides	**Decyl glucoside**
	Surfactants	**Cocamidopropyl betaine**
	Permanent solution	**Glyceryl thioglycolate**
	Emollients	**Octoxyglycerin**
		Dicaprylyl maleate
		Bis-diglycerylpolyacyladipate-2

normally exceed 0.5–1 % for an allergen to be eligible for inclusion in the baseline series (Bruze et al. 1999).

So that follow-up studies in this series, when some allergen does not reach these rates of sensitization, they are usually replaced by a new substance that has increased its response in the last years.

There is often a latency period from the first cases of emerging contact allergens that are observed until an epidemic occurs, and the problem is recognized (Thyssen et al. 2007).

Allergen Groups and Emergent Contact Allergens

The most relevant allergen groups that cause ACD to cosmetics are the following (emergent allergens will be highlighted):

1. **Fragrances**

   Fragrances account for up to 30–40 % of allergic reactions to cosmetics in patients with eczema. The prototype fragrance testing allergen is fragrance mix I, containing eight perfume components, detecting 70–80 % of all perfume allergies.

   Fragrance allergens and ingredients commonly tested in patch test screening include:

   - Fragrance mix 1 (cinnamic alcohol, cinnamic aldehyde, hydroxy citronellal, amyl cinnamaldehyde, geraniol, eugenol, isoeugenol, and oakmoss absolute)
   - Fragrance mix 2 (Lyral, citral, citronellol, farnesol, coumarin, cinnamic aldehyde)
   - Myroxylon pereirae, also known as balsam of Peru

   Limonene is widely used as a fragrance in cosmetics. It is present as a component of certain essential oils (rosemary, peppermint, lemongrass, lavender, eucalyptus, and caraway) and in tea tree oil. Limonene on exposure to air easily oxidizes to products with considerable sensitizing capacity, such as limonene oxide, l-carvone, and the limonene hydroperoxides (Davies and Johnston 2011).

   Oxidized R-limonene has previously been patch tested in multicenter studies, giving 2–3 % positive patch test reactions in consecutive patients. Oxidized R-limonene at 3.0 % (pet) with a specified content of Lim-OOHs 0.33 % is a standardized and useful tool for the detection of contact allergy in dermatitis patients (Bråred Christensson et al. 2013).

2. **Preservatives**

   Preservatives have been identified as common cosmetic allergens in many studies. They are divided into 3 categories: antimicrobials, antioxidants, and UV light absorbers (Table 1).

   2.1 Antimicrobials

   The antimicrobials are used to prevent bacterial and fungal spoilage in topical

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preparations, cosmetics, and personal care products. The main groups of antimicrobials are divided into formaldehyde/formaldehyde releasers and non-formaldehyde-releasing preservatives.

2.1.1 Formaldehyde/formaldehyde-releasing preservatives include:
- Imidazolidinyl urea
- Diazolidinyl urea
- Quaternium-15
- Dimethylol dimethyl (DMDM) hydantoin
- 2-Bromo-2-nitropropane-1,3-diol (bronopol)

2.1.2 Non-formaldehyde-releasing preservatives include:
- Methyl- and methylchloroisothiazolinone mixture
- Parabens
- Methyldibromo glutaronitrile
- Thimerosal
- ***Iodopropynyl butylcarbamate*** (IPBC) is a biocide more recently been incorporated into cosmetic products and cleansing wipes. The maximum permitted concentration is 0.1 %, in these products. In recent clinical study, IPBC continues to be among the less frequent allergens, and a significant relationship between IPBC and thiuram mix allergy was found (further studies are needed to clarify the reason). It is tested to 0.2 %, 0.1 %, and/or 0.5 % pet. (Warshaw et al. 2013).

2.2 Antioxidants

Antioxidants, added to cosmetics to prevent the deterioration of fatty acids such as butylhydroxyanisole, tertiary butylhydroquinone, butylhydroxytoluene, gallates, sodium metabisulfite, and tocopherol/vitamin E, are all potential, albeit somewhat rare sensitizers.
- ***Idebenone*** (hydroxydecyl ubiquinone) is an antioxidant lower molecular weight analogue of coenzyme Q10. Previously, idebenone was shown to be a very effective antioxidant in its ability to protect against cell damage from oxidative stress. Cases of ACD to idebenone following application of antiaging cosmetic cream have been reported, and a patch test with idebenone 0.5 % (pet.) confirmed the diagnosis (Pascoe et al. 2010).

2.3 UV Light Absorbers

There are several sunscreen products on the market that can cause ACD such as para-aminobenzoic acid (PABA), a UV-B blocker, and oxybenzone (benzophenone 3) and avobenzone, both UV-A blockers.

Para-aminobenzoic acid is an early chemical sunscreen agent rarely found today because it was associated with contact and photosensitivity reactions. However, photoallergic dermatitis can be caused by derivatives of PABA and its esters, benzophenones, cinnamates, and dibenzoylmethanes.

2.3.1 Benzophenone
- Benzophenone 3 (oxybenzone), one of the most common photoallergens
- Benzophenone 4 (sulisobenzone)

2.3.2 Cinnamates
- Ethylhexyl methoxycinnamate.
- Octyl methoxycinnamate rarely causes contact dermatitis and is very insoluble in water.
- ***Octocrylene*** (2-ethylhexyl-2-cyano-3,3-diphenylacrylate) is an ultraviolet B-filtering cinnamate that has been increasingly used in the last years; in many countries, benzophenones have recently been replaced by octocrylene as the leading cause of contact dermatitis to sunscreens. Because of its intrinsic stability, it may prevent the photodegradation of other chemical filters such as avobenzone.

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Avenel-Audran et al., in 2010, reported 50 cases of photoallergic contact dermatitis from octocrylene use and/or positive photopatch test reactions to this UV filter. They keep attention to the unexpected association in adults with a history of photoallergic contact dermatitis from ketoprofen. Octocrylene was tested to 10 % (pet.). The researchers observed that octocrylene appears to be a strong allergen leading to contact dermatitis in children and mostly photoallergic contact dermatitis in adults with an often-associated history of photoallergy from ketoprofen. Patients with photoallergy from ketoprofen frequently have positive photopatch test reactions to octocrylene. They concluded that these patients need to be informed of sunscreen products not containing octocrylene, benzophenone-3, or fragrances (Avenel-Audran et al. 2010).

2.3.3 Dibenzoylmethanes

3. **Natural Botanicals**

Topically applied cosmetics and medicaments containing botanical extracts are commonly used. Despite popular beliefs of their benignancy, some botanicals have been implicated in causing allergic contact dermatitis (ACD) in susceptible patients. Specific botanicals implicated in causing cosmetic contact dermatitis include Compositae family plants, tea tree oil, peppermint, lavender, lichens, henna, and others (Jack et al. 2013).

Proteins, most often derived from plants, are common ingredients in cosmetics. Protein derivatives are included in cosmetic creams and (less commonly) in shampoos and conditioners.

3.1 ***Hydrolyzed wheat protein*** (HWP) is the most common protein culprit in ACD, and it tends to cause immediate hypersensitivity. Isolated case reports have described patients with HWP-induced immediate hypersensitivity. Hann et al. reported a patient with contact allergy to hydrolyzed wheat protein found in a cosmetic cream; patch test results were positive at days 2 and 4 with the cream and with a 50 % aqueous solution of HWP (Hann et al. 2007).

3.2 ***Oat and soybean extract*** are another rare cause of ACD.

3.3 ***Propolis,*** also known as bee glue, is a substance collected by worker bees, and it is used as a material for constructing and maintaining their beehives. It is a resinous substance derived from pollens and resins of coniferous, poplar, or other trees and has a variable chemical composition. Propolis is used for its antibacterial and anti-inflammatory effects and is found in shampoo, conditioner, lipsticks, lip balms, lotions, toothpastes, and cosmetics.

The main sensitizers in propolis are 3-methyl-2-butenyl caffeate and phenylethyl caffeate; benzoic, caffeic, cinnamic, coumaric, and ferulic acids are other sensitizers present in propolis. Patch test with propolis is performed at 10 % pet.

Propolis may cross-react with balsam of Peru, with which it shares more than 20 substances and fragrances. Cross-reaction with natural beeswax is unusual, but may occur if beeswax is contaminated with propolis (Davies and Johnston 2011).

4. **Vehicles**

Many of the current vehicles, in particular the water-washable creams and lotions, have a complex formulation composed of many different chemicals such as solubilizers, antioxidants, emulsifiers, preservatives, surfactants, etc.

4.1 Lanolin

Glycols. Glycols are aliphatic dialcohols often used as solvents, preservatives, and humectants in cosmetic products. The prototype of this class, **propylene glycol**

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(1,2-propanediol) (PG), is a colorless, viscous, nearly odorless liquid that is used as an intermediate for the synthesis of other chemicals. It is a multifunctional excipient that is used in many products as a solvent, vehicle, humectant, or emulsifier. Vehicles for topical corticosteroid preparations commonly include PG for enhancing stratum corneum penetration. In addition to topical steroids, PG can also be found in other topical pharmacologic preparations, including antibacterials, antifungals, benzoyl peroxide, and emollients. PG could be an often unrecognized cause of ACD in patients using topical corticosteroids. It is recommended using a 30 % aqueous PG solution for patch testing (Pascoe et al. 2010).

ACD from **1,3-butylene glycol** (1,3-BG) were reported in the Japanese literature. This allergen was found in a cosmetic product, most commonly in creams and lotions but also in hair dyes and lipsticks. Cross-reactions rarely occur between PG and 1,3-BG.

Pentylene glycol (1,5-pentanediol) (PTG) is a solvent, humectant, and preservative that is likely to share, at least in part, the reactivity pattern of PG. Pentylene glycol and PG share similar chemical structure, and a cross-reaction between both compounds might be expected. A 56-year-old woman developed eczematous lesions on the face and eyelids after using a cream and body lotion; both products contain PTG. The patient had a negative patch test result but a positive repeat open application test result with a 5 % aqueous solution of PTG. She was also patch test positive to PG (Kerre 2008).

4.2 ***Alkyl Glucosides***. Glucosides are the condensation products of fatty alcohols, often extracted from palm or coconut oil with glucose. They are used in rinse-off products (e.g., shampoos, soaps, cleansers, hair dyes, and even surgical disinfectants) but also in leave-on products such as lotions, creams, fragrances, sunscreens, and tanning products. Glucosides are chemically closely related to other surfactants, such as methyl glucose dioleate, with which they may cross-react. As well, cross-reactions with other alkyl glucosides such as coco glucoside or lauryl glucoside are likely. **Decyl glucoside** is the most frequent cause of allergic contact dermatitis by this chemical group (Blondeel 2003; Pascoe et al. 2010).

4.3 ***Cocamidopropyl betaine*** (CAPB) is a surfactant derived from coconut oil and dimethylaminopropylamine. It was originally used in "no more tears" formulations and has since been used as a foaming agent in many wash-off personal care products (e.g., shampoos, body washes, toothpaste), an antistatic agent in conditioners and an emulsifier in cosmetics. The actual allergenic molecule in CAPB has not been determined. Amidoamine or dimethylaminopropylamine contamination is considered the most likely cause of allergic reactions to CAPB-containing products.

It has been discovered that all individuals who are allergic to CAPB are sensitized to 3-dimethylaminopropylamine and to amidoamine, molecules which are intermediaries in CAPB synthesis and which persist as impurities in the material that is sold; the amounts vary, depending on the quality of the CAPB in the end product. Betaine is tested at 0.5 % and 1.0 % in pet. (Schnuch et al. 2011).

4.4 ***Glyceryl thioglycolate*** is used in acidic permanent wave solutions, usually in the salon. A similar chemical, ammonium thioglycolate, is used in basic permanent wave solutions and causes allergic contact dermatitis at a much lower rate, although irritant reactions are common. The allergen can persist in treated hair for up to 3 months. The basic permanent wave solutions are also available for home use (Warshaw et al. 2012).

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4.5 **Emollients**

4.5.1 ***Ethylhexylglycerin (octoxyglycerin)*** is an emollient dialcohol. Two case reports described ACD from ethylhexylglycerin. The first patient, a 57-year-old woman presenting with an 8-month history of facial dermatitis, reacted to her facial cream and to one of its ingredients, ethylhexylglycerin (10 % pet.). The second patient was a 64-year-old atopic woman who experienced summer exacerbations of her dermatitis. Ethylhexylglycerin was present in her sunscreen. Patch tests and repeated open application tests confirmed the sensitization. Neither of these patients reacted to PG (Linsen and Goossens 2002).

4.5.2 ***Dicaprylyl maleate*** (DCM), also known as dioctyl maleate, is a good example of an emollient and solvent in which original chemical testing indicated that the compound did not cause ACD. DCM has been used as an ingredient in fake tanning lotions, moisturizers, foundations, and sunscreens.

4.5.3 ***Bis-diglycerylpolyacyladipate-2*** is a semisolid emollient often used as a lanolin substitute. It is valued for its high water-binding properties, excellent adhesion to the skin, and glossy finish. Though it is sometimes contained in cosmetic products such as moisturizer and hair dye, this ingredient is most often used in lip products such as lip gloss, Chap Stick, lip plumper, and lipstick.

Du-Thanh et al. described the first case of ACD with this molecule, in a 35-year-old woman presented with cheilitis and eczema on her cheeks. Patch test with bis-diglycerylpolyacyladipate-2 (16 % pet.) was positive. The compound was present in an antiaging serum heart, a colored envelope, and a powdered eye shadow (Du-Thanh et al. 2011).

Specific Cosmetic Molecules and Emergent Contact Allergens

1. **Copolymers**

Copolymers or heteropolymers are large molecules with high molecular weights (>1,000 D). They have been underestimated for a long time as to their sensitizing capacities. These molecules are used as antistatic, viscosity-increasing, and emulsion-stabilizing agents and can be present in nail lacquers besides many other products.

Approximately 200 copolymers used in cosmetics; seven have caused ACD. Allergic contact dermatitis to six copolymers in cosmetics and one in a medical dressing has been described; however, the nature of the hapten is still unknown.

Quartier et al., in 2006, reported a case of ACD to polyvinylpyrrolidone (PVP)/hexadecene copolymer in a purple-colored lipstick and review the literature on allergic contact dermatitis to seven copolymers: PVP/hexadecene, PVP/eicosene, PVP/1-triacontene, methoxy polyethylene glycol (PEG)-22/dodecyl glycols, methoxy PEG-17/dodecyl glycols, phthalic anhydride/trimellitic anhydride/glycols, and polyvinyl methyl/maleic acid anhydride.

Among these are methoxy polyethylene glycol 17 (PEG-17) and methoxy polyethylene glycol 22 (PEG-22) dodecyl glycol copolymers, which were responsible for an epidemic of ACD in 33 patients. The patients had all used Veet™ (Reckitt Benckiser, Massy, France), an epilating system using warm wax and a soothing moist towel. PEG-22 dodecyl glycol copolymer was one of the ingredients of the moist towel (Pascoe et al. 2010; Quartier et al. 2006).

Polyvinylpyrrolidone (PVP)/eicosene copolymer in a widely used emollient cream has caused a generalized eruption. It also has led to facial eczema in several patients after sunblock use.

Related copolymers such as PVP/1-triacontene or PVP/hexadecene copolymer have caused similar reactions. Polyvinyl methyl/maleic acid copolymer has excellent

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Emergent Allergies in Cosmetics, Table 2

Specific cosmetic molecules	Emergent contact allergens				
Copolymers	PEG-17/PEG 22 dodecyl glycol	PVP/hexadecene PVP/eicosene	PVP/1-triacontene	Trimellitic anh./ phthalic anh. glycol	Polyvinyl methyl/ maleic ac.
Nail products	Methyl methacrylate				
Metals					
Shellac					
Dyes	D&C yellow 11	D&C red 7	Carmine		
Hair care products	PPD				
Lipstick products	Ricinoleic acid derivatives	Diisostearyl maleate	DGS	Isononyl isononanoate	Pentaerythritol rosinate

tackifying and adhesive properties and is used in toothpastes, mouthwashes, denture fixatives, and skin care products. However, the three reported cases of ACD were not due to cosmetics but to peristomal adhesive pastes.

It is believed that impurities, by-products, or degradation products (as water-soluble by-products) are responsible for ACD because copolymers, due to their large size, are unlikely to behave as haptens (Table 2).

Previous studies provide data after using pure PVP in patch testing.

2. **Nail Products and Artificial Nails**

The most common allergen in nail lacquer is tosylamide formaldehyde resin (toluenesulfonamide formaldehyde resin). Even when polymerized and solid, this resin still emits allergenic water-soluble monomers and dimers that are responsible for ACD. Additional allergens in nail lacquer include formaldehyde, ethylene dichloride, phthalates, guanine (crystalline material that produces a shimmering or light-diffusing coloring and it is made from ground-up fish scales), methyl methacrylate, epoxy resin, nitrocellulose, mica (group of hydrous aluminosilicate minerals), polyester resin, amyl acetate, and butyl acetate. Other allergens such as fragrance and sunscreen can be present in the nail lacquer.

The classic presentation is an ectopic dermatitis with involvement of the eyelids, face, head or neck, but other areas (such as the fingers, trunk, and genitals) may be affected at times.

Artificial nails contain acrylates, methyl methacrylate as the main sensitizer. Acrylate monomers (included acrylic acid and its ethyl ester, methyl methacrylate and acrylonitrile) are used to provide elasticity, breaking strength, and transparency, a nail lacquer. Cross-reactions between acrylates are common; therefore, all nail acrylates can cause dermatitis.

Importantly, the use of latex gloves does not protect against acrylates.

As included in previous articles, the patch test concentration and vehicle are recommended for testing contact allergen: monoacrylates 0.1 % pet. and methacrylates monomers 2 % pet. (Jonathan et al. 2011).

3. **Metals**

Eye shadow pressed powder is applied to the skin in the form of talc, and its main ingredients include pigments with nickel, cobalt, chromium, cadmium, zinc, and magnesium stearate (used as binders). Some eye shadows can contain other metal compounds as aluminum, copper, brass, gold, or silver powder used to give metallic brilliant finish.

The concentration of these compounds should be in small amounts and always within safe limits.

4. **Shellac**

Shellac, also known as lacca or gomme-laque, is a resin secreted by the female lac bug, on trees in the forests of India and Thailand. It is processed and sold as dry flakes, which are dissolved in ethyl alcohol to make liquid

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shellac, which is used as a brush-on colorant, food glaze, and wood finish. It is a natural bioadhesive polymer and is chemically similar to synthetic polymers.

Shellac or its wax has many cosmetic uses and is found in pump or aerosol hair sprays, shampoos, eyeliners, mascaras, nail lacquers, and lipsticks.

It is recommended to patch test shellac at a concentration of 20 % in ethyl alcohol. Data from series reported of ACD were limited, but co-sensitization with colophony was present in a few patients (Jonathan et al. 2011).

5. **Fabric Dyes and Pigments**

FD&C dyes and inorganic pigments such as titanium dioxide supply the color. Among dyes, eosin was formerly a notorious allergen and is now rarely used. However, D&C yellow 11 and D&C red 7 have reportedly caused allergic cheilitis.

Carmine is a widely used pigment derived from gravid cochineal insects. Carminic acid is the source of its color. Only three publications describing ACD from carmine could be found. In contrast, there are numerous reports of immediate hypersensitivity reactions from carmine, mostly from its use in foods and beverages but also from cosmetics and pharmaceuticals. These are immunoglobulin E-mediated reactions directed against cochineal proteins.

Suzuki et al. reported a 52-year-old female presented with an itchy erythema on her cheeks at the site where blush had been applied. Patch tested with her cosmetics, she showed a positive reaction to the blush (30 % in pet.) and to 0.2 % (but not 0.1 %) carmine in petrolatum. In this case, the optimum patch test concentration of carmine was 0.2 % in pet. (Suzuki et al. 2011).

6. **Hair Care Products**

Contact allergies to hair dye p-phenylenediamine (PPD) is an important cause of ACD, and it can be found in permanent and semi-permanent hair dyes or added to processed "black henna" (used as cosmetic hair dye and for decorative skin paintings). Other potential allergens in hair products include ammonium persulfate, resorcinol, sunscreens, and fragrance and therefore should be considered for patch testing in the appropriate clinical setting.

7. **Lipstick Products**

The composition of lipstick includes a wax to hold the shape of the lipstick. The wax is usually beeswax, carnauba wax, or candelilla wax. Lipstick ingredients such as shellac (a naturally occurring bioadhesive polymer resin), butylhydroxyanisole, and lanolin are the most frequent allergens involved in allergic contact cheilitis.

An oily base is required to suspend the pigment.

7.1 **Ricinoleic Acid Derivatives**

It is a major component of the seed oil obtained from mature castor plant seeds (castor oil also known as ricinus oil). About 90 % of the fatty acid content in castor oil is the triglyceride formed from ricinoleic acid. It has a very high viscosity, and most pigments are soluble in it. It can be found in lipsticks, makeup, nail lacquer removers, lotions, moisturizers, and soaps. Allergic reactions, which are likely due to free ricinoleic acid, have been reported many times (Pascoe et al. 2010).

Patch test concentration and vehicle recommended for testing contact allergen is undiluted (pure) (Jonathan et al. 2011).

7.2 **Branched-Chain Fatty Acid Esters**

- **Diisostearyl malate is** a branched C-18 aliphatic component. It is a common ingredient in lipsticks, foundations, blushes, eye shadows, creams, and hair conditioners but is present in much higher concentrations in lipsticks than in other cosmetic products.

Another branched-chain fatty acid esters, described as cause of ACD, are glyceryl diisostearate and glyceryl monoisostearate monomyristate.

Hayakawa et al. described an 18-year-old girl who developed cheilitis. Patch testing with the impurities and glyceryl monoisostearate 0.01 % pet. in glyceryl diisostearate and isostearyl alcohol 0.25 % pet. in

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diisostearyl malate was strongly positive (Hayakawa et al. 1987).

- **Isopalmityl Diglyceryl Sebacate** (DGS). This chemical compound was developed in Japan as an alternative to branched-chain fatty acid esters for use as a lipstick base. DGS has hygroscopic properties. It is composed of isopalmitic acid, the hydroxyl radical of diglycerin, and sebacate. Cosmetics that contain DGS are produced in Japan and exported to Korea and Taiwan. The first case report was described in young Japanese women.

  As the molecule is very large, it is unlikely that DGS is the primary antigen. As with TSFR, investigators suspect a smaller-molecular-weight degradation product or by-product to be the culprit (isopalmate) (Pascoe et al. 2010).

  Patch test concentration and vehicle recommended for testing contact allergen with diethyl sebacate is to 5 % pet. (Jonathan et al. 2011).

7.3 **Isononyl Isononanoate**

Isononyl isononanoate is an ester that functions as an emollient, skin-conditioning, and antistatic agent and occur naturally in cocoa and lavender oil. This compound is found in cleanser, serum, moisturizer, liquid foundation, concealer, blush, eye makeup, lipstick, and lip balm.

Goossens et al. in 2008 reported a case of allergic cheilitis caused by isononyl isononanoate present in a lipstick. This patient also reacted to the "anti-cellulite" cream which contained the same ingredient (Goossens et al. 2008).

Patch test concentration and vehicle recommended for testing contact allergen with isononyl isononanoate is to 5 % in alcohol (Jonathan et al. 2011).

7.4 **Pentaerythritol Rosinate** (PER)

PER is an ester of rosin acids derived from rosin (also called **colophony**, is a solid form of resin obtained from pines and some other plants, mostly conifers). It is used as a skin-conditioning and viscosity-increasing agent in mascaras; it creates, upon application, a continuous film on skin, hair, or nails.

This molecule has been described as a cause of ACD in very few cases. There is only one case report of a patient being exclusively allergic to PER; she did not cross-react to rosin (colophony), abietic acid, Myroxylon pereirae, or ester gum (Pascoe et al. 2010).

Additives (such as emollients), antioxidants (such as gallates), and sunscreens are also present, each carrying a potential risk for ACD.

Summary

There are many other forms of cosmetics, including shampoos, toiletry products, moisturizing creams and lotions, and perfumes. Although fragrances and preservatives remain the most common allergens in cosmetics, ADC has also been caused by surfactants, emulsifiers, stabilizers, and sunscreens. Given their versatility, it is not surprising to find in different cosmetic formulations some of the allergens previously described in regard to nail lacquers and lipsticks.

New or unusual cosmetic allergens have been identified in the last few years. Sometimes these allergens are not available in the patch test commercialized, but you should think about them in order to identify and subsequently avoid them.

Patch testing with a broad screening series, supplemented by a patient's own personal care products, should be considered when evaluating patients with suspected cosmetic dermatitis. Once the offending allergen is identified, an avoidance regimen should be established to avoid further exposure.

Cross-References

▶ Allergen Avoidance: Avoidance Strategies for Skin Allergies
▶ Allergic Contact Dermatitis

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- Cobalt Contact Dermatitis
- Contact Allergens Among Children
- Contact Allergy to Black Henna Tattoos
- Contact Allergy to Hair Dyes
- Contact Dermatitis in Children
- Diagnostic Components: Allergen for In Vivo (Skin Testing, Immunotherapy) and In Vitro (Serology) IgE Antibody Testing
- Eyes and Eyelid, Contact Allergic Reaction On
- Fragrance Contact Allergy
- Gold Contact Dermatitis
- Hairdressers' Occupational Skin Disease
- Methods (In Vivo): Skin Test (Intradermal, Puncture)
- Nail Contact Dermatitis, Including Allergic Contact Dermatitis Due to Nail Cosmetics
- Preservatives Contact Allergy
- Protein Contact Dermatitis

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Eosinophil Activation

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Several stimuli, including Ig receptors (especially for secretory IgA [sIgA] and IgG), as well as cytokines (IL-5, GM-CSF, and IL-3), activate the eosinophil. Cross-linking of the IgG receptor,

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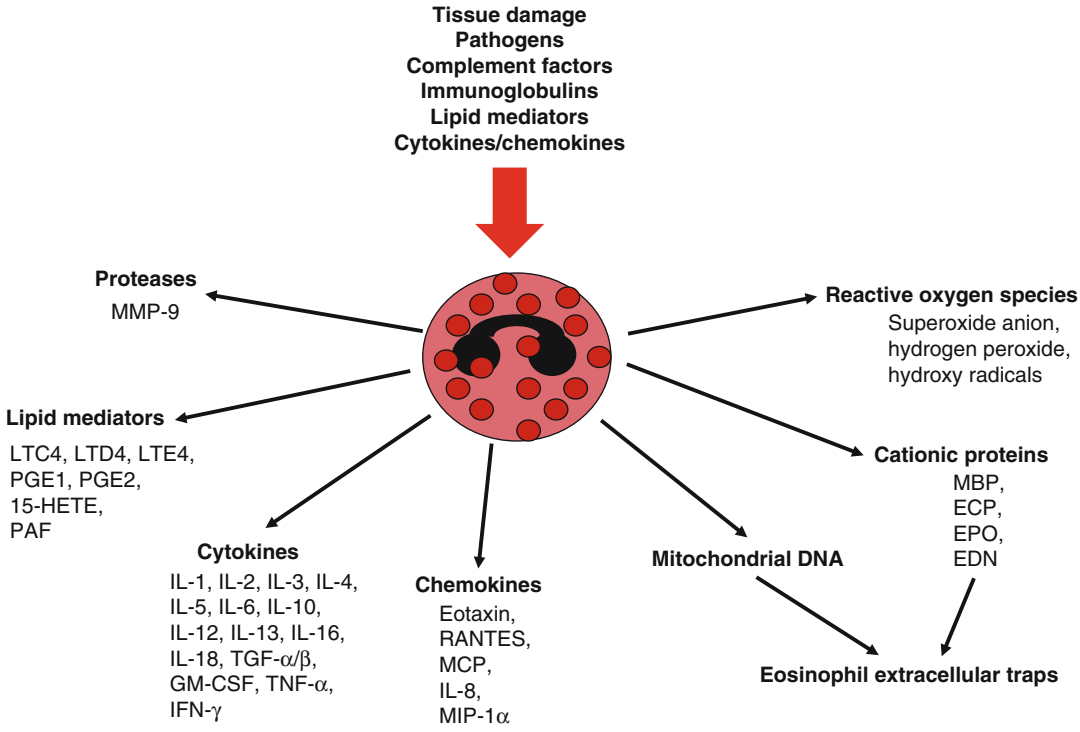

Eosinophil Activation, Fig. 1 Simplified scheme of ▶ eosinophil activation and its multifunctional effects

FcγRII (CD32), enhances eosinophil survival, evidently by autocrine production of GM-CSF, and stimulates apoptosis of adherent eosinophils, through a β2-integrin-dependent mechanism. Secretory IgA is a very potent stimulus for eosinophil degranulation; its potency is mediated by the secretory component, which binds to the eosinophil and synergizes with cytokines or IgG for superoxide production. ▶ Eosinophil activation by cytokines and Igs is critically dependent on β2-integrins, especially Mac-1 (αMβ2). β2-Integrins participate in eosinophil superoxide anion production and in degranulation stimulated by TSLP, PAF, GM-CSF, cross-linking of FcγRII (CD32), sIgA, and IgG (Gleich 2000).

Activated eosinophils generate multiple cytokines (IL-1, IL-2, IL-3, IL-4, IL-5, IL-6, IL-10, IL-12, IL-13, IL-16, GM-CSF, TNF-α, TGF-α, TGF-β, PDGF, VEGF), chemokines (IL-8, eotaxin, RANTES, MCP-2, MIP-1α), lipid mediators (leukotriene B_4, leukotriene C_4, leukotriene C_5, 5-HETE, 5, 15-diHETE and 8, 15-diHETE, 5-oxo-15-hydroxy-6, 8, 11,13-ETE, PGE_1 and PGE_2, 6-keto-PGF_1, thromboxane B2, PAF), and enzymes (Charcot-Leyden crystal protein, 92-kDa gelatinase, collagenase, elastase), as well as reactive oxygen intermediates, superoxide anion, hydrogen peroxide, hydroxy radicals (Fig. 1). There is evidence that different eosinophil subpopulations exist in vivo (Roth et al. 2011).

Cross-References

- ▶ Eosinophil, Definition and Morphology
- ▶ Eosinophil Historical Background
- ▶ Eosinophil Progenitors, Growth, and Differentiation and Death
- ▶ Eosinophil Receptor Expression
- ▶ Eosinophil Recruitment
- ▶ Eosinophils in Disease
- ▶ Hyper-IgE Syndrome

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Eosinophil Granule Proteins

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Eosinophils secrete a range of cytotoxic granule cationic proteins that are able to induce tissue damage and organ dysfunction. The most important of them are: major basic protein (MBP), eosinophil cationic protein (ECP), eosinophil peroxidase (EPO), and eosinophil-derived neurotoxin (EDN). Eosinophil granules contain a crystalloid core composed of MBP and a matrix composed of ECP, EDN, and EPO. MBP, EPO, and ECP are toxic to a variety of tissues, including heart, brain, and bronchial epithelium. ECP and EDN are ribonucleases and have antiviral activity. ECP has been reported to causes pores in membranes of target cells, facilitating the entry of other cytotoxic molecules (Rothenberg and Hogan 2006). Eosinophil granule proteins can also be found in association with extracellular DNA traps in infectious, allergic, and autoimmune diseases (Yousefi et al. 2008).

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- ▶ Hyper-IgE Syndrome

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Eosinophil Historical Background

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Historical Background

A century ago Paul Ehrlich first used the term "eosinophil" to describe this polymorphonuclear leukocyte, although Wharton Jones had first observed its existence in 1846 (Jones 1846). In 1879, Ehrlich stained smears of human peripheral blood cells with acidic dyes and discovered a leukocyte, which strongly bound to acidic dye eosin and therefore named the cell as "eosinophil" (Ehrlich 1879). Paul Ehrlich's staining procedure is still used for examination of peripheral blood. In the early part of the last century, the association of peripheral blood eosinophilia with parasitic and allergic diseases had been established. More recently, a renewed interest in the eosinophil has developed, due to improved knowledge about their biology and specific functions, as well as mechanisms underlying eosinophil-related organ damage. This also resulted in new anti-eosinophil treatment options.

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Eosinophil Progenitors, Growth, and Differentiation and Death

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Eosinophil Progenitors, Growth, and Differentiation

Eosinophils originate from hematopoietic stem cells into a common precursor with shared properties of basophils and eosinophils (CFU-eo/ba), and then separate into eosinophil lineage in the presence of interleukin-5 (IL-5) (Rothenberg and Hogan 2006). Other growth factors for eosinophils are granulocyte-macrophage colony-stimulating factor (GM-CSF) and interleukin-3 (IL-3). These growth regulators are produced and secreted by stromal cells, but also by T cells, mast cells, and eosinophils. IL-3, IL-5, and GM-CSF are all encoded by closely linked genes on chromosome 5q31. Cell surface receptors for IL-3, IL-5, and GM-CSF receptors are detectable on immature multipotent eosinophil progenitor cells, eosinophil-committed precursors, as well as mature eosinophils. Among these three cytokines, IL-5 is most unique to the eosinophil lineage and is responsible for selective differentiation of eosinophils. Deletion of the IL-5 gene in mice causes a marked reduction of eosinophils in the blood and lungs after allergen challenge. Likewise, overproduction of IL-5 in transgenic mice results in profound eosinophilia. Furthermore, anti-IL5 therapy (mepolizumab) has been successful to decrease numbers of blood and tissue eosinophils; however, the latter less efficient (Plötz et al. 2003; Rothenberg et al. 2008; Straumann et al. 2010).

Eosinophil lineage specification is determined by several transcription factors, mainly GATA-1 (a zinc family finger member), and PU.1 (an ETS family member) (Rothenberg and Hogan 2006). These transcription factors are not unique for eosinophils, but their mechanism of action in eosinophils is specific. GATA-1 is clearly the most important transcription factor for eosinophil lineage specification, as revealed by the loss of the eosinophil lineage in mice with targeted deletion of the high-affinity GATA-binding site in the GATA-1 promoter (Yu et al. 2002).

Eosinophil Death

Eosinophils usually die through apoptosis. Under inflammatory conditions, eosinophil apoptosis is delayed, contributing to tissue eosinophilia (Simon et al. 1997). Non-apoptotic eosinophil death, so-called cytolysis and/or autophagic-like cell death, may also occur under some pathological conditions.

Cross-References

- ▶ Eosinophil Activation
- ▶ Eosinophil, Definition and Morphology
- ▶ Eosinophil Historical Background
- ▶ Eosinophil Receptor Expression

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Eosinophil Receptor Expression

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Synonyms

2B4, CD244; Complement receptor 1 (CR1), CD35; Complement receptor 3 (CR3), CD11b/CD18; Complement receptor 4 (CR4), CD11c; Fas receptor, CD95; Inhibitory receptor p60 (IRp60), CD300a; Leukocyte immunoglobulin-like receptor subfamily B member 3 (ILT5/LIR3).

Eosinophil Receptor Expression

Eosinophils express on their surface a variety of cell-surface markers, including adhesion molecules, and chemokine, complement, immunoglobulin, and cytokine receptors. To list all these receptors in detail with their corresponding publications is beyond the scope of this entry. Therefore, the following paragraph will summarize different types of receptors on eosinophils, but the reader may receive more detailed description elsewhere (Rothenberg and Hogan 2006).

Adhesion molecules. Migration of the eosinophil from blood vessels to the inflamed tissue is a multistep process involving rolling, tethering, and firm adhesion. Eosinophils express L-selectin, which regulates eosinophil rolling. They also express E- and P-selectin ligands, various integrins, sialyl Lewis x, intercellular adhesion molecule-1 (ICAM-1), leukocyte function antigen-1 (LFA-1 = CD11a/CD18), as well as leukosialin (CD43) and the leukocyte invasion receptor CD44. Integrins are heterodimeric surface molecules that selectively interact with adhesion receptors, consisting of α and β chain, and eosinophils express members of the β1 (a4b1 and a6b1), β2 (aLb2, aMb2, aXb2, and aDb2), and α7 (a4b7) integrin families. Whereas selectins are considered to mediate rolling and tethering of eosinophils on endothelial cell membranes, integrins and other adhesion receptors mediate firm binding of eosinophils to endothelium prior to transmigration.

Chemokine receptors. Eosinophils constitutively express the chemokine receptors CCR3 and CCR1 and CXCR3. Upon IL-5 activation, CXCR4, CCR5, CCR6, and CCR8 are upregulated.

Cytokine receptors. The most important cytokines for maintenance, differentiation, activation, and viability of eosinophil are IL-3, IL-5, and GM-CSF. Eosinophils express the specific cytokine receptor subunit for IL-3 (IL-3Rα, CD123), IL-5 (IL-5Rα, CD125), and GM-CSF (GM-CSFRα, CD116), as well as the shared β chain (CD131). Eosinophils are also activated upon treatment with stem cell factor (SCF),

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IFN-γ, tumor necrosis factor-alpha (TNF-α), IL-2, IL-4, IL-9, IL-25, IL-27, IL-31, IL-33, and TSLP. Furthermore, eosinophils express a number of IFN receptor superfamily members, including receptors for IFN-α, IFN-β, and IFN-γ.

Complement receptors. Eosinophils express complement receptors for C3a and C5a as well as CR1 (CD35), CR3 (CD11b/CD18), CR4 (CD11c), CD103, and receptors for C1q.

Prostaglandin and leukotriene receptors. Experimental studies have shown that eosinophils express cysteinyl leukotriene receptors (CysLT1R and CysLT2R), high-affinity prostaglandin (PG) D2 type 2 receptor, PAF receptor, as well as histamine H4 receptor.

Immunoglobulin receptors. Eosinophils express Fc receptors for IgA, IgD, IgG, and IgM. The expression of the low-affinity ▶ IgE receptor (CD23) or high-affinity IgE receptors on eosinophils remains controversial.

Other cell-surface structures. Eosinophils express members of the TNF receptor superfamily, such as TNFR1, CD95, and TRAIL receptors. Eosinophils also express CD9, CD37, CD52, CD63, CD81, CD82, and CD151. Under activation conditions, they may also express CD25 and MHC class II.

Inhibitory receptors. Eosinophils express members of the CD2 subfamily of receptors, namely, CD48 and 2B4 (CD244). Eosinophils also express inhibitory receptor IRp60/CD300a, p140, Siglec-3 (CD33), Siglec-8, Siglec-10, ILT5/LIR3, and p75/adhesion inhibitory receptor molecules.

Toll-like receptors. Eosinophils express mRNA for a number of Toll-like receptors (TLR), including TLR1, TLR2, TLR4, TLR5, TLR6, TLR7, TLR8, TLR9, and TLR10.

Cross-References

- ▶ Eosinophil Activation
- ▶ Eosinophil, Definition and Morphology
- ▶ Eosinophil Historical Background
- ▶ Eosinophil Progenitors, Growth, and Differentiation and Death
- ▶ Eosinophil Recruitment
- ▶ Eosinophils in Disease
- ▶ Hyper-IgE Syndrome

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Eosinophil Recruitment

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Under physiological conditions, most eosinophils reside in the gastrointestinal tract, where they normally locate within lamina propria of all segments, except the esophagus (Straumann and Simon 2004). There is a usually a direct correlation between the number of infiltrating eosinophils and disease severity in allergic diseases. Under such pathological conditions, eosinophils equipped with adhesion molecules, such as L- and P-selectins and β1- and β2-integrin molecules, migrate to the sight of inflammation guided by chemokines. Circulating eosinophils lightly tether and roll on endothelial cells by binding to selectins and migrate through the endothelial cells, by traversing the basement membrane barrier and enter the extra-vascular tissue space. The eosinophils (with use of VLA-4 and VLA-6) interact with connective tissue matrix proteins (e.g., fibronectin and laminin) and are exposed to various factors, such as cytokines (e.g., TSLP, IL-5), chemokines (e.g., RANTES and eotaxin), and lipid mediators (e.g., PGD2, cysLTs, PAF), and migrate toward their eventual destination.

Cross-References

- ▶ Eosinophil Activation
- ▶ Eosinophil, Definition and Morphology
- ▶ Eosinophil Historical Background

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▶ Eosinophil Progenitors, Growth, and Differentiation and Death
▶ Eosinophil Receptor Expression
▶ Eosinophils in Disease
▶ Hyper-IgE Syndrome

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Eosinophil, Definition and Morphology

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Definition

Eosinophils are known as myeloid, terminally differentiated granulocytic effector cells that produce and store biologically active molecules, including cytotoxic proteins, lipid mediators, chemotactic peptides, and cytokines. Recently, the knowledge about eosinophil functions has improved and we now consider these cells as multifaceted leukocytes able to modulate both innate and adaptive immunity. Eosinophils are generated in the bone marrow, released to peripheral blood upon maturation, and mainly reside in the hematopoietic and lymphatic organs, such as the bone marrow, spleen, lymph nodes, and thymus. The normal eosinophil blood count ranges from 50 to 500 $\times$ 10^9/L. Eosinophil numbers can increase in various inflammatory reactions, certain hematologic malignancies, and sometimes in patients with solid tumors. Several proposals for the classification of eosinophil-related disorders have been presented (Simon and Simon 2007; Simon et al. 2010).

Eosinophil Morphology

Eosinophils are typically characterized by a bilobed nucleus with highly condensed chromatin. Trilobed nuclei are sometimes seen, whereas multilobed nuclei, comparable to those of adult neutrophils, are rare. The cytoplasm contains two major types of granules, primary and secondary granules, as well as lipid bodies. Primary granules contain Charcot-Leyden crystal protein and eosinophil peroxidase (EPO). Secondary granules are biocompartmental (matrix with a crystalline core) and contain a number of cationic proteins, including eosinophil major protein (MBP), EPO, eosinophil cationic protein (ECP), and eosinophil-derived neurotoxin (EDN) that give the eosinophils the unique staining properties. MBP is confined to the central crystalline core, whereas the other cationic proteins are present in the matrix compartment. The staining characteristic has remained the primary distinguishing feature allowing the identification and quantification of eosinophils in blood and tissues.

Cross-References

▶ Eosinophil Activation
▶ Eosinophil Historical Background
▶ Eosinophil Progenitors, Growth, and Differentiation and Death
▶ Eosinophil Receptor Expression
▶ Eosinophil Recruitment
▶ Eosinophils in Disease
▶ Hyper-IgE Syndrome

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Eosinophilic Esophagitis

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Synonyms

Eosinophilic esophagitis (EE or EoE); Eosinophilic gastrointestinal disease (EGID)

Definition

Eosinophilic esophagitis (EoE) is a chronic, immune/antigen-mediated mucosal disease characterized clinically by symptoms related to esophageal dysfunction and histologically by eosinophil-predominant inflammation (Liacouras et al. 2011).

Cross-References

- ▶ Eosinophil Activation
- ▶ Eosinophils in Disease
- ▶ Food Allergy, Overview

References

Liacouras CA, Furuta GT, Hirano I, Atkins D, Attwood SE, Bonis PA, Burks AW, Chehade M, Collins MH, Dellon ES, Dohil R, Falk GW, Gonsalves N, Gupta SK, Katzka DA, Lucendo AJ, Markowitz JE, Noel RJ, Odze RD, Putnam PE, Richter JE, Romero Y, Ruchelli E, Sampson HA, Schoepfer A, Shaheen NJ, Sicherer SH, Spechler S, Spergel JM, Straumann A, Wershil BK, Rothenberg ME, Aceves SS. Eosinophilic esophagitis: updated consensus recommendations for children and adults [Review]. J Allergy Clin Immunol. 2011;128(1):3.e6–20.e6. quiz 21–2. Epub 7 Apr 2011. PubMed PMID: 21477849.

Eosinophilic Gastrointestinal Disorders

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Synonyms

Eosinophilic esophagitis (EE or EoE); Eosinophilic gastritis (EG); Eosinophilic gastroenteritis (EGE)

Definition

Eosinophilic gastrointestinal disorders (EGID) are chronic, immune/antigen-mediated mucosal diseases characterized clinically by symptoms related to tissue dysfunction and histologically by eosinophil-predominant inflammation.

Basic Characteristics

Background and Prevalence

Although likely cases of EGID have been retrospectively identified as early as the 1950s, recognition of these disorders as a distinct condition only occurred in the late 1990s. However, attempts to specifically define and characterize EGID have been problematic, as these disorders may have protean phenotypic and clinical manifestations, depending on the age and atopic background of the patient and the tissue involved. In addition, EGID can overlap with other disorders in which tissue eosinophilia can be seen, making diagnostic criteria based upon the number of tissue eosinophils difficult. A recent set of consensus recommendations by EGID experts provided an updated conceptual definition of these disorders as chronic, immune/antigen-mediated mucosal diseases characterized

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clinically by symptoms related to tissue dysfunction and histologically by eosinophil-predominant inflammation (adapted from Liacouras et al. 2011). The incidence of EGID has continued to increase, due in part to increasing recognition of these conditions, but also in keeping with the general rise in allergic disorders of all types (e.g., allergic rhinitis, asthma, food allergy) worldwide. Current prevalence in the US population is estimated to be roughly 1 in 10,000.

Pathophysiology

The pathophysiology of EGID involves complex processes that are poorly understood, but are the focus of intense research effort in both murine model systems and humans. The inciting event is thought to be antigen exposure (e.g., food or environmental allergens) in a susceptible host. Following this exposure, a T-helper type 2 (T_H2) immune response ensues that is interleukin-5 (IL-5) dominant, providing eosinophils with their critical growth factor. Immunoglobulin E (IgE) and mast cells are also generally present in the GI tract of affected individuals, supporting the T_H2 dominance of this disease, although their specific roles are unknown in the pathophysiology of EGID. Importantly, the gastrointestinal epithelium dramatically alters its gene expression program in a T_H2-dependent fashion. As part of this transcriptional activation, the epithelium markedly upregulates production of eotaxin-3, as well as a number of other genes, including transforming growth factor (TGF)-β-1, filaggrin, and thymic stromal lymphopoietin (TSLP). Eotaxin-3 appears to be a key chemokine that causes eosinophils to be recruited to the mucosal surfaces of the GI tract (Masterson et al. 2011). Once in the tissue, these eosinophils become activated, releasing a host of cytotoxic mediators and imparting inflammation and tissue damage. The response to this injury involves repair mechanisms that can result in fibrosis and tissue remodeling over time.

Diagnosis

EGID are clinicopathologic conditions, such that the appropriate diagnosis requires characteristic clinical symptoms in association with distinctive histopathologic findings from biopsies of the affected tissue. The clinical presentation varies considerably depending on the age of the patient and the tissue involved. For EoE, common complaints include difficulty swallowing, abdominal pain, and vomiting, which can over time lead to abnormal eating behaviors, including food refusal. If tissue remodeling is present, a food bolus may become lodged in the esophagus and produce a food impaction event. Both EG and EGE can present with abnormal eating behaviors, abdominal pain, nausea, and vomiting; EGE tends to also cause diarrhea and weight loss. Many patients with EGID have other atopic conditions such as eczema, asthma, or environmental allergies, and there is a striking 3:1 male predominance (Wolfe and Aceves 2011).

Endoscopy with biopsy remains the only reliable diagnostic test for EGID, and current recommendations emphasize that multiple biopsies should be taken from multiple sites within the affected organ. Gross findings visualized at the time of endoscopy, such as linear furrowing, whitish exudate, mucosal fragility, and alterations in normal tissue anatomy (e.g., strictures and rings), may be suggestive of EoE, but it is important to note that this is tissue specific and the absence of these findings does not exclude disease. Typical histologic findings may include a dense eosinophilic infiltrate, as well as basal zone hyperplasia, eosinophilic microabscesses, subepithelial fibrosis, extracellular eosinophil granule contents, and other immune cells infiltrating the tissue. The eosinophil infiltrate is typically quantified by the pathologist as an average or peak count of eosinophils seen per high-powered field, which is not by itself diagnostic of EoE since eosinophil recruitment can occur in other disorders, primarily reflux esophagitis. Determining the number of eosinophils that provides optimal sensitivity and specificity for the diagnosis of EoE has proven difficult, although in general 15 eosinophils/hpf (peak value) is considered a minimum threshold for diagnosis, especially when accompanied by some or all of the other pathologic changes mentioned previously (Liacouras et al. 2011).

In contrast, there is no consensus about the number of eosinophils required for the diagnosis

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of EGE, since these cells normally reside in the small and large intestine in healthy individuals; other pathologic findings and clinical context are important clues in making the correct diagnosis (Wolfe and Aceves 2011).

Treatment

Treatments for EGID remain limited to corticosteroids and diet restriction. EoE can effectively be treated with topical corticosteroids such as fluticasone propionate (e.g., swallowing doses from a Flovent™ metered dose inhaler) or oral viscous budesonide, nutritional exclusions, and dilation as needed for strictures. Elemental diets and/or systemic immune suppression with corticosteroids or other immunomodulators is often necessary for EG and EGE (Masterson et al. 2011). There is little evidence that other allergy therapeutics such as mast cell stabilizers and leukotriene antagonists offer clinical benefit. Experimental treatment with biological agents such as anti-IL-5 antibody has been tested, and this or a related approach may prove useful in the treatment of EGID in the future.

Prognosis

EGID are generally considered to be chronic inflammatory disorders that follow a relapsing course. With the appropriate dietary or medical therapy, patients may enter into a period of remission, with resolution of tissue eosinophilia and clinical symptoms. However, symptoms frequently return, especially upon discontinuation of corticosteroid therapy. The long-term pathologic sequelae of EoE appear to chiefly involve esophageal remodeling with stricture, in contrast to reflux esophagitis in which metaplasia and adenocarcinoma can occur with long-standing disease. Detailed longitudinal studies need to be performed in order to better understand the natural history of EGID.

Cross-References

- ▶ Eosinophil Activation
- ▶ Eosinophils in Disease
- ▶ Food Allergy, Overview

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Eosinophils in Disease

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Eosinophils are associated with number of pathogenesis and inflammatory processes, including parasitic helminthes, bacterial and viral infections, bronchial asthma and other allergic diseases, autoimmune diseases as well as malignancies (Simon and Simon 2007). Some of them are briefly discussed below. Under pathological conditions, eosinophil numbers are usually increased in blood and/or tissues, but the pathogenesis may differ and depends on the underlying disease (Simon et al. 1997). Eosinophils are believed to play roles in the defense against pathogens, in the regulation of the immune response, but also in mediating tissue damage and remodeling. For patients with eosinophil-mediated organ pathology, therapeutic intervention with agents reducing eosinophil counts can be effective in limiting organ damage. As newer target agents become available and the understanding of the molecular mechanisms

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driving eosinophilia increases, diagnostic and therapeutic approaches to patients suffering from eosinophilic diseases require modification.

Parasitic infections. The beneficial function of eosinophils has been primarily attributed to their ability to defend the host against parasitic helminths. This is based on several lines of evidence, including the ability of eosinophils to mediate antibody- (or complement-) dependent cellular toxicity against helminths in vitro. The observation that eosinophil levels increase during helminthic infections and that eosinophils aggregate and degranulate in the local vicinity of damaged parasites in vivo makes it likely that eosinophils participate in the protective immunity against selected helminths (Rothenberg and Hogan 2006).

Bacterial infections. Antibacterial activity of eosinophils was mainly concluded because of their phagocytic activity, although this activity is largely limited compared with other phagocytic cells (Beeken et al. 1987). Recent reports suggest that eosinophils exhibit antibacterial activity in the extracellular space. In response to inflammatory triggers, including lipopolysaccharide, complement factor C5a, or eotaxin, eosinophils eject DNA of mitochondrial origin, producing a sticky network that can capture granule proteins and bacteria, which are killed in such extracellular DNA traps (Yousefi et al. 2008).

Viral infections. Eosinophils may also have a protective role against RNA viruses, such as respiratory syncytial virus (RSV). Viral infections enhance mediator release from eosinophils and increase recruitment of eosinophils to the lung after antigen challenge (Gleich 2000).

Asthma. Elevated levels of eosinophil granule proteins such as MBP have been found in bronchoalveolar lavage fluid of patients with asthma. MBP can directly damage lung epithelial cells and is able to activate both mast cells and basophils to release inflammatory mediators. Furthermore, MBP directly increases smooth muscle reactivity by causing dysfunction of vagal muscarinic M2 receptors, which is thought to contribute to the development of airway hyperreactivity (AHR). In addition, eosinophils, by generating large amounts of the cysteinyl leukotrienes, lead to increased vascular permeability and mucus secretion as well as smooth muscle constriction (Rothenberg and Hogan 2006). Eosinophils also play an important role in remodeling of the bronchi.

Gastrointestinal disorders. Besides hematopoietic organs, the gastrointestinal tract is one of the few other human organs, which is physiologically infiltrated by eosinophils. The distribution of the eosinophils is not homogeneous throughout the gastrointestinal tract; the caecal and appendiceal regions have the highest density of eosinophils. Under normal conditions, the esophagus is the only segment of the digestive tract that has no tissue-dwelling eosinophils. Eotaxin has been identified as the primary regulator of eosinophil gastrointestinal homing under noninflammatory conditions. A marked accumulation of eosinophils is seen in several gastrointestinal inflammatory disorders. A subset of these diseases, referred to as primary eosinophil-associated gastrointestinal disorders (EGID), includes eosinophilic esophagitis (EoE), eosinophilic gastritis, and eosinophilic gastroenteritis (Straumann and Simon 2004). EoE has been shown to be an emerging allergic disease (Straumann et al. 2012). Eosinophils seem to contribute to organ dysfunction by both tissue damage and remodeling processes.

Neoplastic diseases. Hematopoietic malignancies are typically associated with eosinophilia. They can represent myeloproliferative and lymphoproliferative disorders, as well as systemic mastocytosis. Some of them can be integrated under the umbrella of hypereosinophilic syndromes. Some solid tumors demonstrate eosinophil infiltration and/or blood (hyper)eosinophilia, whereby the production of TSLP and eosinophil hematopoietins by tumor cells can play a role. The function of eosinophils under these conditions remains unclear.

Cross-References

▶ Eosinophil Activation
▶ Eosinophil, Definition and Morphology
▶ Eosinophil Historical Background

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▶ Eosinophil Progenitors, Growth, and Differentiation and Death
▶ Eosinophil Receptor Expression
▶ Eosinophil Recruitment
▶ Hyper-IgE Syndrome

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Epidemic Contact Dermatitis due to Dimethyl Fumarate

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Synonyms

2-butenedioic acid; Dimethyl ester; Dimethyl ester; *trans*-1,2-ethylenedicarboxylic

Definition

Dimethyl fumarate (DMF) is the methyl ester of fumaric acid. The fumaric acid is a white crystalline substance whose chemical formula is $C_4H_4O_4$. It is one of the two unsaturated isomers of dicarboxylic acid. The other one is maleic acid (Silvestre et al. 2010).

The fumaric acid is an intermediate endogenous compound of citric acid used by cells to get energy to produce adenosine triphosphate (ATP). Besides, it is a product of the urea cycle. Human skin is able to produce naturally fumaric acid after sun exposure (Rostami and Mrowietz 2008).

It is present ubiquitously in the plant kingdom. It is an acid of fruits and used as food additive due to its acidifying property. It is considered not toxic (Silvestre et al. 2010).

Historical Background

In autumn 2006, cases of a peculiar severe dermatitis started to emerge in Finland. Buttocks, back, and posterolateral aspects of thighs or arms were usually the starting location of the itchy and sometimes painful dermatitis. The condition was usually described as being resistant to treatment with even potent topical corticosteroids. Soon, a connection with recliner chairs and sofas manufactured in China was suspected. In February 2007, in a few weeks, tens of cases all over the country were reported in the Internet discussion forum of the Finnish Dermatological Society. A press release of the society and case descriptions in the lay press raised general awareness and brought four more cases. Later, a similar epidemic was reported from the United Kingdom. Patient cases and evidences for a novel contact allergen causing this dermatitis are presented (Rantanen 2008).

In Spain there have been cases with skin involvement since 2007. In the press and on forums, affected cases in relation to footwear have appeared (Fig. 1). Other cases have been published in other areas of Europe that were related also to riding helmets (Magnus 2009).

The Spanish National Institute for Consumer notified the alert of contact dermatitis by DMF

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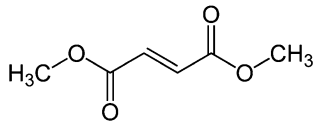

Epidemic Contact Dermatitis due to Dimethyl Fumarate, Fig. 1 Dimethyl fumarate (Dimethyl fumarate structural formulae.png.)

Epidemic Contact Dermatitis due to Dimethyl Fumarate, Fig. 2 Feet dermatitis due to dimethyl fumarate (By courtesy of D. Muñoz)

present in footwear in December 2008 (Official newsletter of the state of January 21, 2009) (Fig. 2).

Epidemiology

The epidemiology of immediate contact reactions by DMF is not well documented. It was implicated as the causative agent in two epidemics of severe acute eczema: sofa dermatitis in northern Europe and shoe dermatitis in Spain (Silvestre et al. 2010).

Fumaric Acid Esters: Uses and Applications

- FA is used as food acidulates since 1946 as it is considered nontoxic. It is also used in the manufacture of plastic, in the production of resins of polyester, and as a mordant for dyes.
- The medical use of fumaric acid esters was first described in 1959 in Germany as systemic treatment of psoriasis (Fumaderm®).

  Other diseases, such as necrobiosis lipoidica, granuloma annulare, and sarcoidosis were also found to respond to treatment with DMF in case reports or small patient series (Meissner et al. 2010).

  Furthermore, treatment with fumaric acid was being evaluated in phase II/III trials for the treatment of multiple sclerosis.
- DMF is an effective mold growth inhibitor, and it has a wide-spectrum biocide activity (D'Erme et al. 2012). It is usually commercially available as a crystalline powder or white granules. The chemical is placed in sachets inside furniture or clothes, as well in shoeboxes, which evaporates and impregnates the products, protecting them from mold (Santiago et al. 2010) and preventing deterioration of products in a moist climate during transport, storing, and importation from the Far East, especially to preserve leather.

Clinical Manifestations

DMF may be responsible of a group of inflammatory reactions that can induce clinical manifestations, such as nonimmunologic contact urticaria (NICU) or nonimmunologic immediate contact reactions (NIICRs) that appear within at concentrations as low as 1 ppm.

NIICRs can occur without previous immunologic sensitization in most exposed individuals. They are the most common type of immediate contact reaction (Lahti 1995). In contrast to NICU, immunologic contact urticaria requires the previous induction of IgE antibody-mediated sensitization to the offending agent, not necessarily through exposure via the dermal route.

The symptoms of NIICRs are heterogeneous, and the intensity of the reaction typically varies, depending on the concentration, the vehicle, the skin area exposed, and the mode of exposure. A further important variable is the susceptibility of the exposed individual, which can vary widely (Basketter and Wilhelm 1996).

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Itching, tingling, and burning accompanied by erythema are the weakest types of reactions. Sometimes, only local sensations without any visible change in the skin are reported. The redness is usually follicular at first and then spreads to cover the whole application site. A local weal and flare suggest a contact urticarial reaction.

Repeated applications of DMF in NICU reactions may cause eczematous reactions. Rapidly appearing microvesicles which can be caused by nonimmunologic (irritant) or immunologic (allergic) mechanisms. In NICU reactions, the symptoms usually appear and remain in the contact area.

In addition to local skin symptoms, other organs are occasionally involved, giving rise to conjunctivitis, rhinitis, an asthmatic attack, or anaphylactic shock (Harvell et al. 1994). This is called the contact urticaria syndrome, and it mostly involves IgE-mediated immunologic mechanisms (Amin et al. 1997).

In some cases, NICU reactions appear only on slightly compromised skin and can be part of the mechanism responsible for the maintenance of chronic eczemas.

After oral Intake of DMF, epigastralgia, vomiting, nausea, and diarrhea have been noted, as well as a flushed face, headache, fatigue, a feeling of warmth, and lymphopenia (Sharon and Elises 2013).

Diagnosis

Patch testing is a safe and fairly reliable method for identifying contact allergens in patients with contact dermatitis (De Groot and Frosch 2011).

DMF can be obtained in hospital pharmacies. The concentration for testing patch should not exceed 0.1 % and may be diluted in an aqueous solution or, if possible, in petrolatum. The adequate concentrations are ranging from 0.01 % to 0.1 % to avoid both false-negative and false-positive (irritant) reactions. Recently, DMF at concentration of 0.01 % in petrolatum has been commercialized (Silvestre et al. 2010).

Patch tests with a piece of the suspected shoe should also be carried out, particularly on the area of the skin with the greatest number of lesions. It is not necessary to moisten the shoe with water, acetone, or other solvents. The test is not always positive in patients allergic to DMF since it depends on whether or not DMF is present in the shoe when the test is carried out. However, in some cases of toxic contact dermatitis caused by DMF, patients do have irritant reactions to patches prepared with samples of the footwear. Tests with sachets of desiccant are not recommended because of the high risk of local irritant reactions. In addition to the DMF patch, a standard battery of skin tests, a specific footwear panel, and an acrylate series should be administered (Silvestre et al. 2010).

Some patients allergic to DMF have been patched with diethyl fumarate, dimethyl maleate, and diethyl maleate, and positive results have been obtained, so it can be concluded that there exists cross-reactivity among the four esters of fumaric acid. It has very relevant clinical importance since acid maleic salt is used in the manufacture of drugs as antihistamines (pheniramine maleate and chlorpheniramine maleate), in the manufacture of plastics, surface coatings, lubricant additives, adhesives, and sealants and chemicals used in agriculture (preservative in oils, in staining and finishing of wool, cotton, and silk).

Management

DMF has a great irritant capacity in contact with skin, and its high sensitizer capacity has been demonstrated.

In the European Union, the use of dimethyl fumarate for consumer products has been forbidden since 1998, and in January 2009, Belgium issued a decree, which bans the placing on the market of all articles and products containing DMF (The Minister for Public Health and the Minister for Consumer Protection 2009). The ban on dimethyl fumarate establishes a maximum concentration of dimethyl fumarate: products containing more than 0.1 ppm (0.1 mg/kg) dimethyl fumarate shall be withdrawn from the market.

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Rapid Alert System for Dangerous Consumer Products (RAPEX) is an instrument of the European Commission that has proven to be useful in reporting new cases of irritant or allergic contact dermatitis associated with DMF (Official Journal of the European Union 2009).

Conclusion

The methyl ester form of fumaric acid named dimethyl fumarate (DMF) is an effective mold growth inhibitor and is used as fungicide to prevent deterioration of products during its transports. DMF has been found to be an allergic sensitizer at very low concentrations, producing eczema that is difficult to treat. It has been responsible for epidemics dermatitis in Finland, the United Kingdom, and in Spain.

In a suspected allergic contact dermatitis of furniture or footwear, it is important to consider DMF as a possible cause of this since this allergen is not included in most series for patch testing. Therefore, patch test with acrylates must be made due to the cross-reactivity with fumaric acid esters.

To avoid contact with DMF, it is very important to take global preventive measures, and they must be developed and applied.

Cross-References

- ▶ Allergen Avoidance: Avoidance Strategies for Skin Allergies
- ▶ Contact Allergy to Shoe Components
- ▶ Occupational Contact Dermatitis Due to Acrylates and Methacrylates

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Epidemiology of Food Allergy

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Synonyms

Prevalence of food allergy

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Definition

Food allergy is defined as an adverse health effect arising from a specific immune response that occurs reproducibly on exposure to a given food (Boyce et al. 2010). In general, it is thought that the peak prevalence of food allergy is approximately 6–8 % at one year of age and then falls progressively until late childhood, after which the prevalence remains stable at about 3–4 % (Sicherer and Sampson 2006). However, in subsequent systematic reviews, it has been stated that food allergy affects between 1 % and 10 % of the population and that it is unclear whether or not the prevalence is increasing (Chafen et al. 2010). The true prevalence of food allergy has been difficult to ascertain for several reasons. Although over 150 foods have been implicated to cause IgE-mediated reactions, most studies only focus on the most common foods. Many of the studies are difficult to compare secondary to their differing study designs and inconsistencies in their definitions of food allergy.

Recent Analyses

A meta-analysis (Rona et al. 2007) on the prevalence of food allergies identified over 50 relevant studies that provided population-based estimates of prevalence. Importantly, these studies had differences in their definition of food allergy. Some used self-reported results (which can overestimate the true incidence of disease), other studies used skin prick testing or food-specific IgE levels, and only a few used double-blind, placebo-controlled food challenges which is the gold standard of diagnosis. In general, studies that used self-reported figures found a higher prevalence of food allergies than studies that used the other three methods. For cow's milk allergy, the pooled estimate of prevalence was 3.5 % from self-report and 0.6 % to 0.9 % from the other three methods. For the other common foods, the pooled estimates for self-report vs. other methods were for egg allergies, 1.3 % versus 0.3–0.9 %; for peanut allergies, 0.75 % versus 0.75 %; for fish allergies, 0.6 % versus 0.2–0.3 %; and for shell fish allergies, 1.1 % versus 0.6 %. When looking at the total prevalence of any food allergy, the overall rates were 12 % self-reported in children and 13 % in adults, 3 % for all ages on the basis of testing and history, and 3 % for all ages on the basis of studies that included double-blind, placebo-controlled food challenges. The authors stated that the precision of these latter estimates was very poor. They recommended more standardized methods for diagnosis to decrease the large variability across studies.

In a systematic review of the prevalence of plant food allergies including fruits, vegetables, legumes, tree nuts, wheat, cereals, soy, and seeds (Zuidmeer et al. 2008), investigators included 36 studies with data from a total of over 250,000 children and adults. Analyses were based on self-perception, test results, and oral food challenge, but only six studies included the latter. Among the few studies including oral food challenges, prevalence ranged from 0.1 % to 4.3 % each for fruits and tree nuts, 0.1 % to 1.4 % for vegetables, and <1 % each for wheat, soy, and sesame. When evaluating reported symptoms or skin tests, the ranges varied from almost 0 to 4.2 % for fruits, 2.7 % for vegetables/legumes, 4.5 % for tree nuts, 1.2 % for wheat, and 0.6 % for soy. Similar to the Rona et al. study, there was a significant heterogeneity between studies regardless of food item or age group. They stated that "[p]opulation-based prevalence estimates for allergies to plant products determined by the diagnostic gold standard are scarce," and "[t]here was considerable heterogeneity in the prevalence estimates of sensitization or perceived allergic reactions to plant food."

Since the release of the previous mentioned studies, there have been new population-based data that add to this discussion. Investigators studied a birth cohort born on the Isle of Wight in the United Kingdom between 2001 and 2002 prospectively (Venter et al. 2008). Children were clinically examined and skin prick tested at set times and invited for food challenges when the food had not been eaten and positive tests were identified, or if an adverse reaction was reported.

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The cumulative percentage of complaints of adverse food reactions was 33.7 % at 3 years, with 8 % having a current complaint, with systems involved being cutaneous, followed by gastrointestinal, and more rarely respiratory. Using unblinded oral food challenges and a clear history, the cumulative incidence was 6 %. Using the gold standard of double-blinded, placebo-controlled food challenges, the incidence was 5 % and the primary triggers were milk, egg, and peanut. A study based in Denmark (Osterballe et al. 2009) evaluated 1,272 young adults aged 22 years by using questionnaires, skin prick tests, and oral food challenges. By questionnaire, 20 % reported adverse reactions to non-pollen-associated foods, which after oral food challenge (performed in 25 % of those subjects with complaints) resulted in a prevalence of 1.7 %. These two studies again show the gross overestimation of food allergy using only self-reported data.

Food Allergy and Other Atopic Disease

An association between early food allergy and later atopic respiratory conditions has been noted in multiple studies (Nickel et al. 1997; Høst and Halken 1990; Hattevig et al. 1984; Sigurs et al. 1994). A child with food allergy has between a 50 % and 90 % chance of subsequently developing asthma. Young children who are sensitized to food in infancy, particularly egg, often develop subsequent sensitization to aeroallergens. In one study, an egg-specific IgE greater than 2 kU/L in combination with a positive family history of atopy translated into a highly specific (specificity, 99 %) and predictive (positive predictive value, 78 %) marker for sensitization to inhalant allergens at 3 years of age (Nickel et al. 1997). In another study of Danish infants, those with cow's milk allergy and early IgE sensitization to cow's milk had an increased risk of the development of persistent adverse reactions to other foods (38 %), particularly egg white (29 %), and inhalant allergy (48 %) before 3 years of age. Finally, in a Swedish study of 324 children followed prospectively from birth found that sensitization to foods in infants was associated with appearance of IgE antibodies to inhalants later in life, with the most likely food culprit being egg white (Sigurs et al. 1994).

Changes in Prevalence

When looking at data analyzing the rate of any food allergy over time, there are only a few studies. In a study comparing results from two cross-sectional studies from the same clinic in Chongqing, China, performed in 1999 and 2009, food challenge-proven rates of food allergy increased from 3.5 % to 7.7 % (Hu et al. 2010). Investigators looked at data from several national databases in the United States where information could be compared over time (Branum and Lukacs 2009). They found that in 2007, 3.9 % of US children < 18 years of age had reported food allergy. The prevalence of reported food allergy (not confirmed with any objective data) increased 18 % from 1997 through 2007.

There have been several studies specifically looking at the changing prevalence of peanut allergy over time. A random-calling telephone survey was performed looking at peanut and tree nut allergy across the United States using the same methodologies in 1997, 2002, and 2008 (Sicherer et al. 2010). The rates of surrogate-reported allergy in children increased significantly for tree nuts (0.6 %, 1.2 %, and finally 2.1 %) and for peanut (0.4 %, 0.8 %, and finally 1.4 %). Limitations of the studies included self-report, decreasing participation rates, and self-assessment of allergy with an inability to control for increasing awareness as an explanation. Data from the previously mentioned Isle of Wright cohort point to a different conclusion (Grundy et al. 2002; Venter et al. 2010). Peanut sensitization and allergy rates were reported from three birth cohorts from this locality. Comparison of the cohort born in 1989 and 1994–1996 showed a nonsignificant twofold increase in reported peanut allergy (Grundy et al. 2002). After analysis that included oral challenges, the total

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estimate for clinical peanut allergy was 1.5 % among the 1994 to 1996 cohort. A following publication (Venter et al. 2010) compared these results to a third cohort born between 2001 and 2002 from the same geographic location and found reaction rates of 1.2 %, indicating a leveling off or slight decline. In summary, for overall food allergy, there is evidence for an increase in food allergy prevalence, as has been noted for other atopic conditions, but confirmatory studies are lacking. For peanut allergy, there are mixed results regarding an increase.

Rates of Serious Allergic Reactions

A population-based study analyzing data from Rochester, Minnesota, USA, looked at the years 1990–2000 (Decker et al. 2008). They found the overall rate of anaphylaxis was 49.8 per 100,000 person-years. They also found an increase in the annual incidence rate during the study period from 46.9 per 100,000 persons in 1990 to 58.9 per 100,000 persons in 2000. Food ingestion-related anaphylaxis accounted for 33.2 % of these cases. Foods were found to be the most likely indentified culprit, with insect stings being the next most frequent. Caution should be used when extrapolating this particular data to a larger population since this study only looked at one specific geographic location. Investigators looking at data from the US National Electronic Injury Surveillance System identified emergency department events describing food-related allergic reactions from 34 participating hospitals from August 1 to September 30, 2003 (Ross et al. 2008). Extrapolation of this data predicted a total of 20,821 hospital ED visits, 2,333 visits for anaphylaxis, and 520 hospitalizations caused by food allergy in the United States during the 2-month study period. No deaths were reported.

Rates of deaths related to food allergy have only been examined indirectly. Extrapolating from a series of population-based studies of Olmstead County, Minnesota, USA, investigators predict that there are about 29,000 anaphylactic episodes due to food allergy in the United States each year, resulting in about 150 deaths (Bock et al. 2001). That would translate into a 0.5 % fatality rate of anaphylactic episodes per year. Using codes listed on death certificates in Florida over a 10-year period, an annual anaphylaxis fatality rate was determined to be 5 in 10 million (Simon and Mulla 2008). A food trigger was noted in 16 % of these cases. Extrapolation from this study would estimate roughly 1 in 12 million deaths from food allergy (Sicherer 2011).

Conclusion

Food reactions can occur for many reasons, but food allergy is caused by a specific immune response. Although a significant percentage of people report adverse food reactions, the rates of verifiable food allergy are much lower. Challenges to determine the prevalence of food allergy include differing definitions of food allergy and inconsistent methodologies used for measurement. In general, it is thought that the peak prevalence of food allergy is approximately 6–8 % at one year of age and then falls progressively until late childhood, after which the prevalence remains stable at about 3–4 %. However, in other studies, it has been stated that food allergy affects between 1 % and 10 % of the population. Young children who are sensitized to foods or have confirmed IgE-mediated food allergy (especially egg) are more likely than their nonallergic counterparts to later develop other atopic diseases. There is compelling evidence for an increase in food allergy prevalence, as has been noted for other atopic conditions, but confirmatory studies are lacking.

Cross-References

- ▶ Anaphylaxis, Clinical Manifestations and Diagnosis
- ▶ Atopic Dermatitis
- ▶ Cow's Milk Allergy
- ▶ Diagnostic Terms: Atopy

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▶ Egg Allergy
▶ Food Allergy, Overview
▶ Peanut Allergy

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Etiology of Anaphylaxis

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Definition

The most common triggers of anaphylaxis are foods, venom of stinging insects, and drugs; there are, however, a number of other important causes, as detailed in Box 1. Foods are the most common trigger in infants, children, and young people, but these will be outgrown in many cases. Drugs and the venom of stinging insects are the

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most common in adults (Alves and Sheikh 2001). Some patients experience anaphylaxis due to idiopathic causes.

Box 1: Causes of Anaphylaxis

Common

- Foods: most commonly peanuts, tree nuts, hen's eggs, seafood, cow's milk, and seeds
- Medications: most commonly antibiotics, nonsteroidal anti-inflammatory drugs, opioids, and neuromuscular blocking agents
- Insect stings: most commonly bees, hornets, wasps, and fire ants
- Idiopathic

Less common

- Physical triggers (e.g., exercise, cold)
- Biological fluids/preparations (e.g., transfusions, immunoglobulin, antivenoms, semen)
- Latex
- Tick bites
- Hormonal changes: breastfeeding, menstrual factors
- Dialysis membranes (hemodialysis-associated anaphylaxis)
- Hydatid cyst rupture
- Aeroallergens: domestic/laboratory animals, pollen
- Food additives: monosodium glutamate, metabisulfite, preservatives, colors, natural food chemicals
- Topical medications (e.g., antiseptics)

Source: EAACI Guidelines (in press)

Cross-References

- ▶ Anaphylaxis, Background
- ▶ Anaphylaxis, Clinical Manifestations and Diagnosis
- ▶ Biphasic, Protracted, and Late-Phase Reactions in Anaphylaxis
- ▶ Management of Anaphylaxis
- ▶ Mast Cell Mediators Associated with Anaphylaxis
- ▶ Pathophysiology of Anaphylaxis

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Exercise Challenge

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Synonyms

Treadmill test

Definition

Exercise challenge is a form of indirect bronchial challenge that is commonly used in the diagnosis of exercise-induced bronchoconstriction or exercise-induced asthma.

Essay

There are two types of challenges, direct and indirect, which are discussed in further detail in the separate entry entitled: *Bronchial Challenges*. The exercise challenge is an indirect challenge, which means that exercise acts via inflammatory cells of the airway to indirectly cause bronchoconstriction in a susceptible patient. The exercise challenge is often used to determine whether respiratory symptoms that develop during exercise are caused by bronchoconstriction. An electrocardiogram can be done during the challenge to ensure that there are no cardiac rhythm changes during exercise that might be accounting for the symptoms. Similarly, a laryngoscopy can be performed

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immediately following the exercise portion of the challenge to ensure that exercise-induced vocal cord dysfunction is not the cause of a patient's symptoms.

In an effort to better standardize this test, the American Thoracic Society (ATS) published guidelines for exercise challenges in 2000 (Crapo et al. 2000). These guidelines recommend a warm-up period, followed by 6 min of near-maximal exercise while breathing relatively dry and cool air (less than 50 % relative humidity and less than 25 °C) on a treadmill or stationary bike. Colder air can be used in select patients. The goal heart rate should be 80–90 % of the predicted maximum, which is defined as 220 minus age beats per minute. A baseline FEV1 is obtained prior to starting exercise and at 5-min intervals following exercise until a sufficient drop in FEV1 occurs or 30–45 min have elapsed since the start of the test, whichever comes first. The exact interval of testing following exercise varies between centers.

An exercise test is considered positive for exercise-induced bronchoconstriction if the FEV1 drops by 10 % or greater, with some centers using more stringent criteria of a 15 % decline in FEV1. Some investigators factor in the immediate post-exercise improvement and calculate a "lability index" incorporating the immediate rise and subsequent fall in FEV1. Because the exercise challenge involves near-maximal exercise with no assessment until after exercise, it has the potential to drop the lung function of very reactive patients quite rapidly and dramatically. Therefore, this challenge should be done in a closely monitored setting. Patients who demonstrate bronchoconstriction during the test are given a dose of bronchodilator following the test, and a repeat spirometry is performed to ensure a return to baseline (Cockcroft 2008).

For a discussion of contraindications to bronchial challenges, which have been specifically defined for methacholine challenge, please see the separate entry entitled: *Bronchial Challenges*. Medications that might interfere with test results and how long these medications should be held prior to testing are topics discussed in the entry entitled: *Methacholine Challenge*.

Cross-References

▶ Bronchial Challenges

References

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Exhaled Nitric Oxide

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Synonyms

eNO; FeNO

Definition

Exhaled nitric oxide is a test that measures the fractional concentration of exhaled NO (FeNO) in order to assess underlying allergic/eosinophilic inflammation in the lungs of atopic asthmatics.

Introduction

The exhaled nitric oxide test, which measures the fractional concentration of exhaled NO (FeNO), is a relatively new tool in the assessment of asthmatic patients. In this entry, the scientific background for the test, practical aspects of FeNO

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measurement and interpretation, and the implications for clinical use of this test are discussed.

Scientific Background

Nitric oxide (NO) is an inert gas that is produced primarily by cells of the cardiovascular and respiratory systems and is generated from L-arginine through the action of an enzyme called NO synthase (NOS) (Ricciardolo et al. 2004; Forstermann et al. 1991). There are three NOS isoforms formed by various cells of the respiratory tract, two of which are constitutively expressed: NOS1, originally known as nNOS, since it was thought to be mainly expressed by neuronal cells, and NOS3, originally known as eNOS given its expression in endothelial cells. The third NOS enzyme, known as NOS2 or iNOS because it is inducible, is thought to be expressed continuously at low levels by human airway epithelial cells under normal conditions but also upregulated by proinflammatory cytokines and stimuli (Guo et al. 1995; Fischer et al. 2002).

In the lower airways of normal individuals, constitutive iNOS levels are relatively low and considerably lower than the levels found in the upper airway. Studies have shown, however, that allergen exposure leads to an increase in the level of iNOS in the respiratory epithelium of asthmatic and atopic patients, both at the mRNA level and the protein level, when compared with normal controls. The pathophysiologic basis for this increase is thought to be possibly related to the effects of cytokines known to be key players in the allergic response, such as IL-4 and IL-13 (Fig. 1) (Alving and Manlinovschi 2010).

Given this correlation between allergic cytokines, iNOS upregulation, and NO production, FeNO levels are thought to represent underlying allergic inflammation. One subset of allergic inflammation is that which is caused by the eosinophil, a cell that is prominent in a large subset of asthmatic patients. Several studies have shown a correlation between FeNO and eosinophilia in induced sputum, bronchoalveolar lavage, and tissue (Berlyne et al. 2000; Jatakanon et al. 1998; Warke et al. 2002; Brightling et al. 2003; Payne et al. 2001; Van den Toorn et al. 2001), although this correlation seems to be strongest for tissue eosinophilia (Alving and Manlinovschi 2010).

FeNO Measurement

Since FeNO technology is relatively new, it is not readily available in many community pulmonary or allergy clinics. In centers that do have a FeNO measurement device, the test is relatively easy to perform and can sometimes be performed in patients as young as 4 years old. It requires that a patient first create a good seal around a mouthpiece connected to the FeNO machine. Once on the mouthpiece, they fill their lungs to total lung capacity (TLC) with air that is free of NO and then breathe out at a steady rate for approximately 6 s, which is the time necessary for the FeNO level to plateau. When the patient exhales, they do so against a positive pressure that causes the velum to close, which serves to exclude the upper airway NO and hopefully limit the FeNO measurement to the lower airway. The rate at which a patient exhales can affect the level of FeNO, with faster flow rates causing a decrease in FeNO and vice versa. As such, machines need to be set at a consistent flow rate in order to allow for comparison from one clinical setting to another. The standard flow rate as determined by the American Thoracic Society (ATS) and the European Respiratory Society (ERS) is 50 mL/s (Silko et al. 1997, 2000; ATS/ERS 2005).

FeNO Interpretation

There are several intrinsic and extrinsic factors that can either increase or decrease FeNO levels, as shown in Table 1. These factors must be taken into account when interpreting test results (Alving and Manlinovschi 2010; Kharitonov et al. 1995; Carraro et al. 2008; Papi et al. 2006).

In part because of these many variables, comparing FeNO levels between different patients

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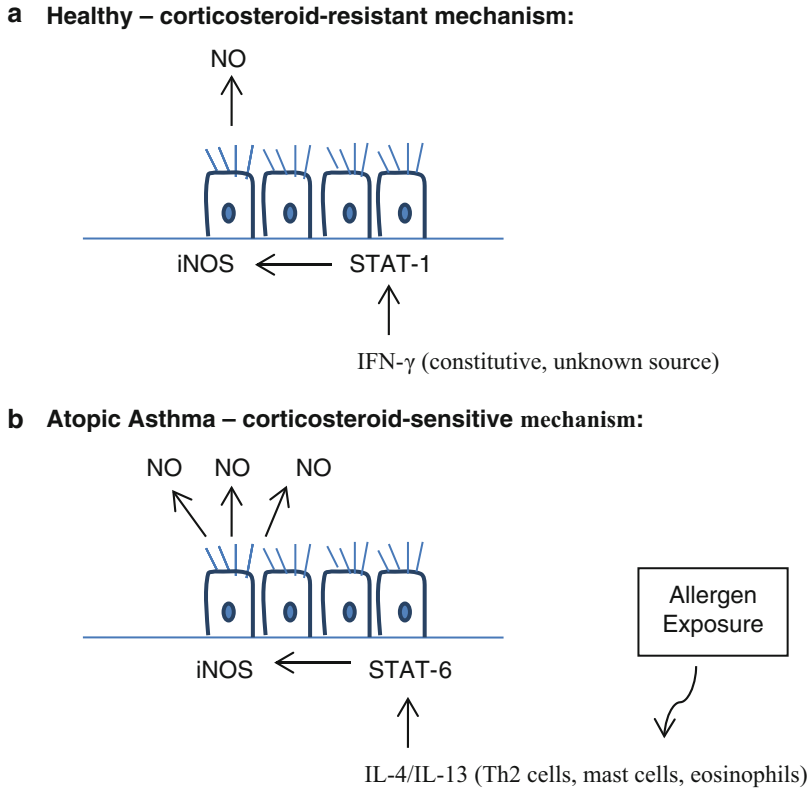

Exhaled Nitric Oxide, Fig. 1 Pathophysiologic mechanism for increased NO production in the lower airways of healthy controls (**a**) versus patients with atopic asthma (**b**). Note that the asthmatic airway also demonstrates STAT-1-mediated constitutive iNOS expression in addition to the inducible STAT-6-mediated upregulation shown here (Adapted from Alving and Manlinovschi 2010)

Exhaled Nitric Oxide, Table 1 Factors that affect FeNO levels (Data taken from reference Alving and Manlinovschi 2010; Dweik et al. 2011)

Decrease FeNO	Uncertain effect	Increase FeNO
Current smoking	Weight/BMI	Male gender
Past smoking	Menstrual cycle	Height
Bronchial provocation	Physical exercise	IgE sensitization/allergen exposure
Dietary antioxidants	Spirometric maneuvers	Recent dietary intake of nitrate
Bacterial infections	Age (in adults)	Age (in children)
Respiratory syncytial virus (RSV) and influenza virus	Diurnal variation	Holding one's breath between inhalation and exhalation maneuvers during test
		Rhinovirus infection
		Air pollution – ozone or particulate matter

becomes difficult, as does establishing community norms for FeNO. Several studies have been performed to this end (Buchvald et al. 2005; Olin et al. 2006; Kovesi et al. 2008), all with slightly different normal ranges and mean values for children, men, and women. The current recommendation for interpreting FeNO is to utilize the clinical cut points shown in Table 2, although these cut points have yet to be well validated (Dweik et al. 2011).

When interpreting FeNO levels, it is also important to keep in mind a patient's current asthma therapy. Those medications that target airway inflammation, especially corticosteroids,

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Exhaled Nitric Oxide, Table 2 Clinical cut points currently recommended for FeNO interpretation (Data taken from Dweik et al. 2011)

	Adults	Pediatrics
Eosinophilic inflammation unlikely	<25 ppb	<20 ppb
Unclear, depends on clinical context	25–50 ppb	20–35 ppb
Eosinophilic inflammation likely, usually steroid responsive	>50 ppb	>35 ppb

Exhaled Nitric Oxide, Table 3 The effect of long-term asthma therapy on FeNO (Data taken from reference Alving and Manlinovschi 2010)

Medication	Effect of therapy on FeNO
Corticosteroids (oral >> inhaled)	Marked decrease
Leukotriene receptor antagonists	Slight decrease
Omalizumab (anti-IgE receptor antibody)	Decrease
Chromones (e.g., cromolyn)	No effect
Methylxanthines (e.g., theophylline)	No effect

will decrease FeNO levels, whereas other asthma medications have no effect on FeNO (Table 3) (Alving and Manlinovschi 2010).

For patients on inhaled corticosteroid (ICS) therapy, therefore, persistently elevated FeNO levels on follow-up might indicate that they are not using their ICS as prescribed or that they require a higher dose of ICS to control their degree of airway inflammation. Patients who are on an adequate dose of ICS and are taking the medication as prescribed will generally see normalization of their FeNO levels, assuming that there are no other confounding factors present. Having said this, there does seem to be a small subset of atopic asthmatic patients whose FeNO does not normalize on corticosteroid therapy, although the reason for this is not well understood (Stewart and Katial 2012).

Application of FeNO to Clinical Practice

As a tool in the management of asthma, FeNO is still relatively new. The American Thoracic Society (ATS) recently published guidelines on the use of FeNO. These guidelines conclude that FeNO measurement can provide advantages in "(1) detecting of eosinophilic airway inflammation, (2) determining the likelihood of corticosteroid responsiveness, (3) monitoring of airway inflammation to determine the potential need for corticosteroid, and (4) unmasking of otherwise unsuspected nonadherence to corticosteroid therapy" (Dweik et al. 2011). The first of these conclusions stems from the strong correlation between FeNO levels and underlying allergic or eosinophilic inflammation, as described above. The remaining conclusions originate in the understanding that corticosteroids are very effective in decreasing this type of inflammation, thereby lowering FeNO levels. Several studies have demonstrated that patients starting out with a higher FeNO level are more likely to respond to corticosteroid therapy (21 miles ref # 48–50), and at least one study showed a trend toward higher FeNO in patients with poor medication adherence (Katsara et al. 2006).

Perhaps the most important aspect of incorporating FeNO into clinical practice, therefore, involves choosing the appropriate patient to receive the test. Although FeNO levels are generally elevated in poorly controlled or severe atopic asthma (Delgado-Corcoran et al. 2004; Meyts et al. 2003), these levels are usually normal in nonatopic patients, even in those individuals with severe or poorly controlled asthma (Alving and Manlinovschi 2010). Similarly, patients with stable COPD do not have elevated levels of FeNO, although these levels do tend to increase during exacerbations or in patients with unstable COPD (Robbins et al. 1996; Corradi et al. 1999; Maziak et al. 1998). As such, FeNO could be used, in combination with clinical history and other testing, to help distinguish atopic asthma from other conditions, such as nonatopic asthma or COPD, for patients with stable respiratory symptoms and an obstructive pattern on spirometry.

Although establishing community norms for FeNO has proven difficult, FeNO levels can be tracked within a given patient over a time. Doing so can help assess asthma control and medication

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adherence and can even assist in guiding therapeutic decisions. FeNO levels are particularly useful in patients who are poor perceivers of their symptoms since an elevated FeNO may indicate ongoing or increasing inflammation before a patient actually perceives an increase in symptoms. For these patients, therapy could be increased earlier in hopes of decreasing an impending exacerbation, particularly once a pattern of FeNO measurements in relation to clinical status has been established. Several studies have been performed to determine the feasibility and impact of a FeNO-guided approach to asthma management, with mixed results depending on study design and primary outcome (Smith et al. 2005a, b; Pijnenburg et al. 2005; Szefler et al. 2008).

Summary

FeNO is a biomarker that is quick and easy to obtain and serves as an indirect measure of atopic and/or eosinophilic inflammation of the lower airways. For many patients with atopic asthma, it can aid in diagnosis as well as in the assessment of disease severity, response to treatment, phenotypic categorization, and adherence to treatment regimens. As discussed above, there are many caveats to the use of FeNO, and it should therefore be used in conjunction with other established measures of asthma control.

Cross-References

- Analytes and Biomarkers: Nitric Oxide (NO) and Asthma
- Eosinophil Historical Background
- Eosinophils in Disease
- Testing: Sputum Eosinophil Count

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Eyes and Eyelid, Contact Allergic Reaction On

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Synonyms

Allergic contact dermatitis; Allergic contact eczema; Periocular dermatitis; Periocular eczema; Periorbital dermatitis; Periorbital eczema

Nomenclature and Definition

Contact allergy of the eyelid represents an inflammatory skin disease due to an antigen-specific T-cell-mediated immune response. Referring to the classification of allergic reactions published by Coombs and Gell (Gell and Coombs 1963), contact allergy is classified as "delayed-type" T-cell-mediated hypersensitivity reaction. Immediate-type reactions of contact allergy have also been reported, but are rare.

Clinical Features

Contact allergy of the eyelids occurs in patients who developed sensitization to an antigen they previously have had (repeated) skin contact to. Depending on the course, acute and chronic allergic contact dermatitis can be differentiated. Clinical symptoms of acute allergic contact dermatitis are redness of the periorbital skin combined with swelling, which might also affect the conjunctivae (Fig. 1). In very severe cases, small blisters (vesiculae) as well as crusting and oozing may be apparent on the eyelids as well (Niebuhr et al. 2011; Werfel and Kapp 2006).

In the absence of a sufficient anti-inflammatory treatment and in cases in which skin contact to the causing allergen continues

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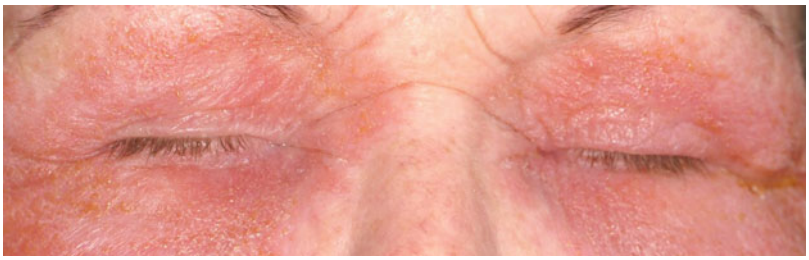

Eyes and Eyelid, Contact Allergic Reaction On, Fig. 1 Acute allergic contact dermatitis of the eyelids and the periorbital region

chronic contact dermatitis may develop persisting over weeks, months, or even over several years. It is characterized by less redness and swelling, but visible thickening of the skin (lichenification) and scaling. Both acute and chronic allergic contact dermatitis is associated with severe itch (pruritus) and therefore cinch marks (excoriations) may be present at each stage of the disease.

Prevalence

Women suffer more frequently from contact allergy of the eyelids than men (Cooper and Shaw 2000) that is also due to the eliciting allergens (e.g., greater use of cosmetics).

Differential Diagnoses

Contact allergy has been identified as one of the main causes for periorbital dermatitis (Feser et al. 2008). However, in patients with atopic dermatitis periorbital eczema is frequently observed as well. Although periocular eczema represents a typical clinical manifestation of atopic dermatitis per se, it has been demonstrated that atopic diathesis represents a risk factor for periocular dermatitis and in cases of persistent, refractory periocular dermatitis the relevance of contact allergy, which may then act as a trigger factor of atopic dermatitis, should be considered. Periocular psoriasis vulgaris and conjunctivtis allergica as well as drug intolerance and seborrheic dermatitis represent further possible differential diagnoses involving the periorbital region as well (Feser et al. 2008).

Pathogenesis

Contact allergy of the eyelid is due to an antigen-specific T-cell-mediated immune response (Peiser et al. 2012; Kimber et al. 2002; Wittmann and Werfel 2006; Martin et al. 2011), which is reviewed in the chapter of allergic contact dermatitis. Since sensitized T-cells clonally proliferate upon allergen exposition and are not restricted to the tissue of the origin of the dendritic cells but rather are present in the circulation as well, skin symptoms of contact allergy may not only be restricted to the area of direct skin contact. A characteristic clinical sign of allergic contact dermatitis is therefore the spreading of inflammatory efflorescences. This may occur following extensive allergen exposition, in cases where the causing allergen has a high capability to penetrate into the skin or in highly sensitized patients. Of note, these clinical and immunological phenomena cannot be observed in non-allergic irritant contact dermatitis.

For several years investigation of contact allergy particularly has focused on the relevance of activation of the innate immune system for contact allergic reactions. While it could be demonstrated that contact allergens are able to activate cells via toll-like receptors, it is discussed whether infections may support the development of sensitization to contact allergens (Martin et al. 2011).

Diagnostic Procedures

The diagnosis of periorbital allergic contact dermatitis is based on the patient's history and on a patch test including standard allergens and,

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according to the patient's history (e.g., greater use of cosmetics in the periorbital region by women), individually selected contact allergens. Regarding the procedure of patch testing the reader is referred to the respective guideline of the German Society of Dermatology "Performing a patch test with contact allergens" (Schnuch et al. 2008; Feser and Mahler 2010).

Regarding the evaluation of patch test results it should be emphasized that the skin of the eyelid is more sensitive than the skin area in which patch tests are performed (uninvolved skin of the back). Therefore, in cases of eyelid eczema the possibility of false-negative patch tests results should be considered (Schnuch et al. 2009). For this reason, in cases of suspected contact allergy with involvement of the eyelid a modification of the patch test is recommended including tape stripping before the test allergen is applied to the skin.

Allergens and Allergen Sources

Clinical studies evaluating patch test results in patients suffering from eyelid dermatitis revealed not only age of 40 and older, atopic skin conditions but also a higher proportion of women demonstrating a greater cosmetic use (Feser et al. 2008). Regarding the facial regions in more detail it has been found that those patients with eyelid and facial involvement more often suffered from allergic contact dermatitis than those with eyelid involvement alone (Cooper and Shaw 2000). Sensitization to nickel (II) sulfate can commonly be observed in patients with periocular eczema. Cosmetics applied in the periorbital region such as eyelash curlers, make-up base, and eye shadow have been identified as frequent sources of relevant contact allergens. These products also contain nickel (II) sulfate. However, the clinical relevance of a positive patch test result to nickel (II) sulfate for periorbital dermatitis is still discussed, but is recommended to be evaluated in individual cases (Feser et al. 2008). Further relevant contact allergens are fragrance mix and balsam of Peru. Preservatives in medical solutions should be considered as possible allergen sources as well. Of these, thiomersal not anymore represents a relevant preservative used for cosmetic products or for medical products such as eye drops and contact lens solutions. A higher frequency of positive patch test results in patients with periorbital dermatitis has been found to neomycin sulfate (Feser and Mahler 2010). The topical use of kanamycin sulfate has also been demonstrated be associated with a very high risk for allergic contact dermatitis (Uter et al. 2009). In cases of eyelid dermatitis which is due to airborne contact dermatitis air fresheners and nail polish might be the relevant allergen source (Feser and Mahler 2010). A higher frequency of positive patch test results has also been observed to para-phenylendiamin, which can be found in cosmetics such as mascara and hair tinting lotions (Temesvári et al. 2009).

Treatment

Identified allergens need to be avoided. In case of aeroallergens, this might be difficult, depending on the presence of the respective allergen. Symptomatic treatment includes topical corticosteroids of low potency (since the periorbital skin is very thin and thus an increased risk of skin atrophy exists) or topical calcineurin inhibitors such as pimecrolimus and tacrolimus.

Cross-References

- ▶ Allergic Contact Dermatitis
- ▶ Atopic Dermatitis
- ▶ Contact Dermatitis Due to Topical Drugs
- ▶ Contact Allergy to Hair Dyes
- ▶ Diagnostic Components: Allergen for In Vivo (Skin Testing, Immunotherapy) and In Vitro (Serology) IgE Antibody Testing
- ▶ Diagnostic Components: T Helper Cell Cytokines (IL-4, IL-5, IL-9, IL-10, IL-13, IL-17)
- ▶ Diagnostic Terms: Atopy
- ▶ Emergent Allergies in Cosmetics
- ▶ Fragrancy, Allergic Contact Dermatitis
- ▶ Hairdressers' Occupational Skin Disease
- ▶ Nail Contact Dermatitis, Including Allergic Contact Dermatitis Due to Nail Cosmetics

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► Nickel Allergic Contact Dermatitis
► Occupational Contact Dermatitis Due to Acrylates and Methacrylates

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F

Fatal Allergic Reactions to Foods

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Synonyms

Allergic reactions to foods; Anaphylaxis; Severe anaphylactic reactions to foods

Definition

Fatal allergic reactions to foods: Death directly attributable to the physiologic consequences of an IgE-, mixed IgE-/non-IgE-, or non-IgE-mediated hypersensitivity resulting from the ingestion of a food antigen. Physiologic consequences include the following in isolation or combination: hypovolemic shock from GI fluid loss in non-IgE-mediated allergy, respiratory collapse from angioedema or bronchospasm in IgE-mediated allergy, and distributive shock from vasodilation and/or volume redistribution in IgE-mediated allergy.

Epidemiology

An estimated 150–200 annual deaths in the United States are directly attributable to anaphylactic reactions to foods (Sampson 2003). Per the United Kingdom (UK) fatal anaphylaxis register, 2.3 deaths per 100,000 people age 15–24 with nut allergies were attributed to anaphylactic reactions to peanuts or tree nuts. The median age at the time of the fatal allergic reaction was 21 years (Pumphrey 2004). Sixty-nine percent of fatal reactions occurred in patients between the ages of 13 and 21 years (Sampson et al. 2006). No overall difference in the ratio of fatal allergic reactions to foods between males and females has been identified. However, some studies have illustrated a higher ratio of females to males having fatal reactions to nuts (Pumphrey 2004). There is no apparent difference in the incidence of fatal allergic reactions among racial groups as studied in the United Kingdom (Pumphrey 2004). Data on fatal non-IgE-mediated food allergy reactions, such as food protein-induced enterocolitis (FPIES), is lacking.

Causes

Nuts cause the highest proportion of fatal allergic reactions. Causes of 31 identified fatal reactions in the United States between 2001 and 2006 included peanut (17), tree nuts (8), milk (4), and shrimp (2) (Bock et al. 2007). Causes in the United Kingdom from 1992 to 2004 included peanuts (10), other or unidentified nuts (22), milk (5), fish (2), chickpea (2), shellfish (2), banana (1), and snail (1) (Pumphrey 2004). Milk tended to be the cause in younger children with

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a median age of 8 years with nuts as the cause in older children and adolescents (Pumphrey 2004). A case study of six fatal reactions of five girls and of one boy age 2–16 years attributed three of the deaths to peanut ingestion, two to other nuts, and one to egg (Sampson et al. 1992).

Characteristics of Fatal Reactions

Physiologic manifestations and symptoms associated with fatal anaphylaxis are often limited to one system. The actual cause of death can often be classified as either shock or respiratory arrest. Respiratory symptoms are often the first sign of a potentially severe food-induced reaction (Eigenmann et al. 2008). Case reviews have illustrated that respiratory collapse is the most common cause of death in fatal allergic reactions to food (Pumphrey 2004). Fatal distributive shock after standing during severe anaphylaxis has been reported (Pumphrey 2003). This is believed to result from a fatal redistribution of volume away from the heart, a phenomenon termed "empty ventricle syndrome." It is important to note that the severity of previous reactions and time elapsed since previous reactions do not help in predicting those in which fatal or near-fatal allergic reactions are likely. Fatal reactions often occur in those in which previous reactions were mild (Pumphrey and Gowland 2007). The time between ingestion of the causative food and fatal collapse is usually between 25 and 35 min. In one study, this time ranged from 10 min to 6 h. The longest of which followed initial administration of epinephrine and a period of stabilization (Pumphrey 2004). Many patients with fatal allergic reactions had experienced previous reactions to the same foods. In one study not only did the time since the previous documented reaction vary from 2 weeks to greater than 5 years, these patients also lacked a history of previous severe allergic reactions (Sampson et al. 1992). A large portion of fatal reactions occurs in teenagers and young adults. Risk-taking behaviors in this group including failure to carry IM epinephrine because of embarrassment or tight clothing and knowingly eating allergen-containing foods because of peer pressure are among the identified contributing factors (Sampson et al. 2006). Presentations of non-IgE-mediated reactions such as FPIES are often severe. These reactions can be confused with sepsis. Without aggressive volume resuscitation, fatal hypovolemic shock can occur.

Association with Asthma

Multiple case reviews have established an association between asthma with severe allergic reactions to nuts (Sicherer et al. 2001). The majority of reported cases of fatal allergic reactions to foods occurred in patients considered to be highly atopic. Asthma appeared to be the most consistent manifestation of atopy in these patients. The degree of asthma control varied between reports. The majority of fatal reactions in one study were asthmatic reactions in people requiring daily medications for asthma control (Pumphrey 2004). Noncompliance with daily asthma controller medications such as inhaled corticosteroids and overuse of short-acting beta-2 agonists is a common finding in these cases. Short-acting beta-2 agonists may lead to epinephrine resistance. It is believed that aggressive asthma control with daily-inhaled corticosteroids will optimize the chances of recovery from a severe anaphylactic reaction where the airways are involved (Pumphrey 2004). It has been suggested that females of college age with asthma and a nut allergy living away from home are at an increased risk of fatal or near-fatal allergic reactions to nuts (Pumphrey 2004).

Prevention

IM epinephrine should be made available for all patients with IgE-mediated food allergy. A 2006 case series identified only 4 of 31 patients who had fatal allergic reactions to foods had IM epinephrine administered within a reasonable time (Bock et al. 2007). Aggressive control of asthma

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is essential in optimizing airway function. This will assure patients as much respiratory reserve as possible during a severe anaphylactic reaction. During an anaphylactic reaction, patients should remain supine until all symptoms of anaphylaxis have resolved completely. Proper patient and caregiver teaching concerning avoidance of allergen ingestion, signs of anaphylaxis, and proper administration of medications are necessary to ensure correct and rapid intervention. Other identified factors contributing to fatal reactions were denial of symptoms by patients or caregivers, reliance on oral antihistamines, and delay in epinephrine administration (Yunginger et al. 1988). Patient education about cross-contamination and how to read food labels is also important. Special attention must be given to those patients believed to be at higher risks of fatal reactions, i.e., teenagers and young adults. It has been identified that teens with food allergy would benefit from peer education concerning their condition by decreasing teasing and peer pressure as well as increasing the numbers of those able to provide help in emergent situations (Sampson et al. 2006).

Cross-References

- Allergic Proctocolitis and Food Protein-Induced Enterocolitis Syndrome (FPIES)
- Cow's Milk Allergy
- Diagnostic Components: Allergen for In Vivo (Skin Testing, Immunotherapy) and In Vitro (Serology) IgE Antibody Testing
- Diagnostic Food Challenges
- Diagnostic Terms: Atopy
- Egg Allergy
- Eosinophil Activation
- Food Allergens
- Food Allergy, Overview
- Food Desensitization
- Nutrition in Food Allergy
- Oral Allergy Syndrome
- Peanut Allergy
- Specific IgE

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Fingernails from Sensitization to Acrylic, Loss of

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Synonyms

Acrylates; Contact dermatitis

Acrylates are synthetics produced out of derivates from acryl acid and are very potent inducers of delayed-type hypersensitivity sensitization. They can be found in adhesives, paints,

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dental prosthesis, bone cement, and artificial fingernails. Prolonged or repeated exposure to these materials can result in pronounced allergic contact dermatitis. In case of allergic reactions to acrylates in synthetic fingernails, periungual inflammation can harm the nail matrix, thus leading to temporary loss of the natural nail. To ensure regrowth, strict avoidance of the responsible contact allergen is necessary.

Cross-References

▶ Allergic Contact Dermatitis

Food Allergens

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Synonyms

Atopic foods

Definition

A food allergen is defined as a protein that the immune system recognizes as nonself and elicits allergic symptoms (i.e., flushing, urticaria, shortness of breath, wheezing, emesis, diarrhea). Allergic symptoms will typically develop within minutes to an hour of ingesting the allergenic protein; however, the allergy to galactose-alpha-1,3-galactose in meat can be delayed for up to four hours (Commins et al. 2009).

Food allergy as defined by the National Institute of Allergy and Infectious Diseases expert committee is "an adverse health effect arising from a specific immune response that occurs reproducibly on exposure to a given food" (Boyce et al. 2010). This reaction can be immunoglobulin E (IgE) mediated (e.g., oral allergy syndrome) or non-IgE mediated (e.g., food protein-induced enterocolitis syndrome, which is thought to be T cell mediated). This entry will focus primarily on IgE-mediated response to food allergens, which is a type I hypersensitivity reaction in which B cells secrete IgE that binds to mast cells. Mast cells degranulate in the presence of certain food proteins identified as allergenic and trigger a TH2-mediated inflammatory cascade. The immune-mediated paradigm of TH1 versus TH2 cellular cascade has prevailed until recently, when the roles of other cells such as T-regulatory cells (Tregs) have been considered important components of the allergic immune response (Braga et al. 2011).

Despite there being more than 150 foods linked to IgE-mediated food allergies (Allen 2012), the vast majority of food allergies are generally attributable to eight food allergens: milk (cow's), soy, egg (hen's), peanuts, tree nuts, wheat, fish, and shellfish (Sicherer 2012). The allergenicity of these foods is related to their ability to dissolve in water, resistance to heat and digestion, glycosylation (which gives the protein the ability to more effectively resist proteolysis), high concentration of allergenic protein, and low molecular weight (Martos et al. 2011; Vickery et al. 2011).

Natural History

Food allergies are a growing global health concern. A study of nearly 3,000 infants in Australia confirmed greater than 10 % were sensitized to a common food allergen by the age of 1 year (Osborne et al. 2011). In the United States, Rona et al. performed a systematic review of fifty publications and estimated the prevalence of self-reported food allergies among adults and children to be 13 % and 12 %, respectively (Rona et al. 2007). Prevalence rates that are not supported with laboratory data and are based solely on self-reports have been shown to be unreliable. When self-reports are confirmed by skin prick testing, serum IgE (sIgE), or double-blind, placebo-controlled food challenges (DBPCFC), the overall prevalence of food allergy in United States drops to 2.5–3 % (Boyce et al. 2010; Liu et al. 2010). Although

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the prevalence of food allergies had been reported to be rising based on random digit phone surveys (Sicherer et al. 2003), surveillance data now suggests that it has remained stable and may be anywhere from 1 % to 10 % (Chafen et al. 2010).

For decades, it had been known that atopic dermatitis conferred a higher risk of developing food allergies (Sampson 1983). More recently, an extensive population-based analysis suggests that a diagnosis of asthma, being male, under the age of 19, and being a non-Hispanic black are also significant risk factors for the development of a food allergy (Liu et al. 2010). Except for allergies to peanuts, tree nuts and crustaceans, most food allergies do not persist past adolescence (Waserman and Watson 2011).

Diagnosis

The gold standard for diagnosing a food allergy is by DBPCFC. This can be a laborious process, as it is typically performed on multiple days. A less costly, but less invasive, alternative is skin prick testing (SPT), which is performed at an allergist's office in about 15 min and has a negative predictive value of greater than 90 % (Mahoney et al. 2011). The test works by detecting allergen-specific IgE that is produced by B cells. The extent of the allergic response appears to be correlated with the ability of certain epitopes in the allergen to bind to IgE in allergenic foods (Vickery et al. 2011). The larger the size of the allergen molecule, the more B cells which become activated and the more robust the polyclonal IgE response.

Allergen-specific sIgE can also be measured to increase the positive predictive value of skin testing, and may even be preferred over SPT in certain instances (i.e., eczema flare, inability to stop taking antihistamines 1 week prior to testing). A sIgE is usually detectable within the first 2 years of life, and a decline can be indicative of tolerance, i.e., sIgE < 2 (Boyce et al. 2010). Even in the absence of food allergen, subjects who remain allergic will continue to produce IgE, thus explaining the sensitivity of skin prick testing as a diagnostic tool and the importance of analyzing serum or skin prick tests with clinical symptoms. Of note, different testing modalities, e.g., ImmunoCAP vs. Immunlite, will not necessarily calculate the same sIgE level (Boyce et al. 2010), so it is less helpful to compare values from different modalities over time than from the same modality.

Clinical History of the "Big Eight" Food Allergens

Cow's Milk

The primary allergens identified in cow's milk include whey and caseins, specifically beta-lactoglobulin and alpha-lactalbumin in the whey family, and alpha S1, alpha S2, and beta-caseins (Mills 2012). Because of their high degree of homology, there is a high risk of cross-reactivity between caseins and whey in cow's milk and other mammals (i.e., sheep and goat), which means that the risk of developing an allergic reaction to cow and sheep milk is high (Clare Mills et al. 2012). The risk of an allergic reaction is increased when beta-lactoglobulin is heated with lactose or ingested with oil, but actually reduced when baked (Clare Mills et al. 2012).

Cow's Milk allergy is the most prevalent food allergy and is estimated to be higher in children than in adults, ranging anywhere from 2 % to 7 % (Allen 2012; Boyce et al. 2010). Resolution generally occurs by age 15 (Host et al. 2002), which explains the lower estimated prevalence of 1–2 % in adults (Boyce et al. 2010).

Most often, it presents with emesis, constipation, and failure to thrive. Because it can also be a non-IgE-mediated allergy, the onset of symptoms may be delayed. It is associated with other comorbidities such as gastroesophageal reflux, proctocolitis, and eosinophilic esophagitis (Allen 2012).

The diagnosis is definitively made when all cow's milk protein is removed from a person's diet and symptoms resolve, but can also be made reliably by SPT in children (Sicherer and Sampson 2010). In terms of treatment, oral immunotherapy (OIT) and sublingual immunotherapy (SLIT) were shown to induce desensitization in cow's milk-allergic children after 14 months of therapy,

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although the effects were not long-lasting (Keet et al. 2012). In a study of 66 cow's milk-allergic children, early exposure to cow's milk as a supplement to maternal breast milk appeared to promote tolerance (Katz et al. 2010). The American Academy of Pediatrics (AAP) encourages exclusive breastfeeding of infants until 4–6 months of age, if a child has a high risk of atopy (Greer et al. 2008). The AAP also discourages the consumption of soy milk, citing a risk of cross-reactivity in 14 % of cow milk-allergic infants, and instead promotes extensively hydrolyzed formulas in cow milk-allergic children who are not breastfed (Bhatia and Greer 2008).

Egg

The major allergens in egg are found in the white of the egg and include Gal d 1 (ovomucoid) and Gal d 3 (ovalbumin) (Bernhisel-Broadbent et al. 1994; Clare Mills et al. 2012).

Egg allergy is second to milk in prevalence, affecting about 1–2 % of children (Lemon-Mule et al. 2008). Early exposure to egg by six months of age seems to reduce the likelihood of developing an allergy to egg (Wang and Sampson 2011). Similar to milk, egg is typically outgrown prior to adulthood, but perhaps not as early as previously believed. In a study of 881 egg-allergic patients, 68 % developed tolerance by age 16 (Savage et al. 2007).

The process of heating ovomucoid with gluten-containing products has been shown to reduce its allergenicity (Clare Mills et al. 2012). Recent work intended to elucidate the effects of heat on ovomucoid has revealed that the process thwarts the ability of the allergen to activate basophils and T cells in the gut, decreasing its digestibility (Martos et al. 2011). A promising study found that children who consumed small amounts of cooked egg shifted away from an allergic phenotype toward a tolerant state (after three months of treatment, they had smaller SPT results and increasing ovalbumin- and ovomucoid-specific IgG4 levels) (Lemon-Mule et al. 2008). The same study found that subjects with sIgE levels $\geq$ 50 kU/L remained egg allergic.

Egg allergy poses a dilemma for the clinician when it comes to vaccinations – whether to administer the influenza and the measles, mumps, and rubella/varicella (MMR, MMV) vaccines, which are cultured in chick embryos and contain ovalbumin. Multiple approaches to vaccination have been studied, which include administration in divided doses, administration after a SPT has been verified, and administration of a vaccine with smaller amounts of ovalbumin. In terms of the flu vaccine, experts recommend vaccinating children with egg allergies, who do not have a history of egg anaphylaxis or severe reactions (e.g., angioedema), for influenza (2011a, b, c; Boyce et al. 2010). The reasoning is that the egg protein content of this vaccine is quite low and the infectious risk of the disease outweighs the risk of an allergic reaction. On the other hand, children who have a history of egg anaphylaxis should be administered the MMR and MMRV vaccines, and preferentially the monovalent varicella vaccine because it contains no egg protein (Boyce et al. 2010).

Peanut

The major peanut allergens include Ara h 1–11 (IUIS 2012). The process of boiling diminishes peanut allergenicity and may explain the variable prevalence within a genetically similar population that eats boiled peanut in China and roasted peanut in the United States (Beyer et al. 2001).

Peanut consumption in the United States has increased by 20 % over the last two decades, and the prevalence of peanut allergy doubled in five years, reaching 0.6 % (Boyce et al. 2010; Burks 2008). A survey of American households found that three million Americans suffer from peanut or tree nut allergies and that eight of every 1,000 children under the age of five are allergic to peanuts (Sicherer et al. 2003). Unfortunately, only 20 % of children will outgrow their peanut allergy by age three (Scurlock and Burks 2004). Although most peanut-allergic children who ingest peanut typically experience non-life-threatening reactions, in a cohort of 83 children with peanut hypersensitivity, 44 % had potentially life-threatening reactions upon reexposure (Vander Leek et al. 2000). This alludes to the difficulty children face when trying to avoid peanut, as it is commonly used as an additive in

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foods and trace amounts can be inadvertently ingested. OIT and SLIT have shown promising results in skewing the immune system toward a nonallergic state. In a study of 29 peanut-allergic children who underwent OIT, 93 % were able to ingest 3.9 g of peanut without adverse effects (Jones et al. 2009).

Tree Nuts

Tree nuts most associated with food allergies include almonds, Brazil nuts, cashews, chestnuts, hazelnuts, macadamia nuts, pecans, pine nuts, pistachios, and walnuts. Their major allergens are members of the prolamin and cupin superfamily, such as the 2S albumins, cupin seed globulins, and 11S and 7S seed storage globulins (Breiteneder and Clare Mills 2005; Clare Mills et al. 2012). More recently, oleosins in sesame and hazelnut have been discovered to be major allergens (Clare Mills et al. 2012). The cupin seed globulins are also found in legumes such as pea and peanut, but have been found to have minimal IgE cross-reactivity between them (Breiteneder and Clare Mills 2005). There is evidence to suggest, however, that there is cross-reactivity between peanut and tree nuts at the T cell level (Kulis et al. 2009).

Tree nut allergy affects 0.5 % of children under 18 years of age and 0.3 % of adults (Sicherer et al. 2003). It is outgrown in only 9 % of cases, but once it resolves, it has not been shown to recur (Byrne et al. 2010; Fleischer et al. 2005). About half of individuals who have a tree nut allergy are allergic to more than one tree nut, hazelnut is the most common worldwide (Preedy et al. 2011), and walnut is the most common among US children (Sicherer et al. 2003) but is also common in other cohorts (Fleischer et al. 2005). Chestnut accounts for a small number of tree nut allergies but has come under close scrutiny as it has been identified in latex-allergic individuals. The widespread use of latex gloves by healthcare workers during the AIDS pandemic in the 1980s is associated with the rise in the incidence of chestnut allergy (Blanco 2003). The explanation for this relationship is thought to lie in the cross-reactivity between Cas s 5, the major allergen in chestnut, though more recent evidence points to IgE to the Hev b 8 (profilin) allergen (Radauer et al. 2011; Raulf-Heimsoth et al. 2007).

Individuals, in particular young children, who are allergic to tree nuts are often encouraged to avoid peanuts and vice versa. A study of over 1,000 subjects found that only 58 % of adults and 24 % of children were able to correctly identify 19 nuts, and there was no difference found between allergic and non-allergic subjects (Hostetler et al. 2012). Consequently, strict avoidance and epinephrine injections remain the mainstay of treatment for tree nut allergy. For those who are considering an oral challenge to confirm tolerance, an accepted cutoff is a tree nut sIgE $\leq$5 kU/L (Fleischer et al. 2005).

Although strict avoidance remains the mainstay of tree nut allergy, emerging data by Kulis et al. suggests that it may be possible to induce tolerance to cross-reacting allergens. The group showed that when tree nut-sensitized mice underwent immunotherapy with a single tree nut, their allergic response to cross-reacting tree nuts was diminished (Kulis et al. 2011).

Wheat

The major wheat allergens include seed storage prolamins and α-, β-, γ-, ω-gliadins (Akagawa et al. 2007; Clare Mills et al. 2012). In wheat, the allergens that have been identified include gliadins and wheat germ agglutinin (Tri a 18) (Radauer et al. 2011; Sander et al. 2011).

The prevalence of wheat allergy in children is estimated to be 0.3–0.5 % (Kotaniemi-Syrjanen et al. 2010). Similar to milk and egg, a wheat allergy is generally outgrown by adolescence. A retrospective study of 350 food-allergic children found 8 % to be allergic to wheat – this was confirmed by SPT or sIgE and oral challenge (Kotaniemi-Syrjanen et al. 2010). Subjects were followed for 7 years and by age 16, nearly all (96 %) tolerated wheat. Additional findings from this hallmark study include the discovery that a SPT <5 mm to wheat is a reliable threshold for passing an oral challenge and that SPT reactivity to wheat was significantly ($p = 0.001$) associated with birch pollen SPT reactivity.

Wheat allergy has also been linked to a higher risk of asthma (Kotaniemi-Syrjanen et al. 2010;

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Panzani et al. 2008). This is not surprising, as Baker's asthma has long been known to be an occupational peril among bakers, millers, and farmers. Baker's asthma is an IgE-mediated allergy, typically resulting from the inhalation of barley and rye. In a study comparing French and Spanish bakers, those with higher IgG4 and IL-10 levels had significantly greater symptom control (Panzani et al. 2008).

Fish

The major food allergens in fish are Seb m 1 and Xip g 1, which are parvalbumins (IUIS 2012; Clare Mills et al. 2012). Unlike other common food allergens, parvalbumin is a hardy protein that resists high temperatures and lysis. The process of smoking (Bernhisel-Broadbent et al. 1992; Clare Mills et al. 2012) seems to increase its allergenicity by creating new allergenic structures, whereas canning diminishes its allergenicity (Bernhisel-Broadbent et al. 1992). A study in Australia has challenged the accepted notion that there is cross-reactivity between fish and crustaceans (2006; Turner et al. 2011); however, this is not endorsed by the American College of Allergy, Asthma and Immunology (2006).

A random telephone survey of the United States estimates the prevalence of fish allergy to be 0.5 % among adults and 0.2 % among children (Sicherer et al. 2004). It commonly presents in adulthood and is unlikely to be outgrown.

Shellfish/Crustaceans/Mollusca

The major shellfish allergen, tropomyosin, is found in crustaceans and mollusca (Clare Mills et al. 2012). Prevalence of shellfish allergy is 1.2 % by self-reports but drops to 0.6 % when confirmed by SPT or sIgE (Boyce et al. 2010). Similar to fish allergy, shellfish allergy typically presents in adulthood. A mean wheal diameter of 20–30 mm has a 95 % PPV for a positive DBPCFC (Jirapongsananuruk et al. 2008). Interestingly, tropomyosin is also found in cockroaches and dust mites (Yang et al. 2010). This common link may explain the rise in shellfish allergies among inner-city children who are exposed to a high load of cockroach and dust might allergens.

Soy

Gly m 1–6 have been identified as major allergens in soy protein (IUIS 2012). Prevalence of soy allergy, when confirmed by food challenge, has been estimated to be 0.7 % of the US population (Boyce et al. 2010). Two-thirds of soy allergic children outgrow their allergy by age seven (Savage et al. 2010). However, those with sIgE >50 kU/L have only about 18 % likelihood of outgrowing their soy allergy (Savage et al. 2010).

Research into cross-reactive allergens has found that Gly m 4 is as a major allergen in soybean-allergic and birch pollen-allergic individuals (Holzhauser et al. 2009; Mittag et al. 2004). Because soybean cross-reacts with birch pollen, as the trend toward consuming soy rises globally, soy allergy may be expected to rise.

Conclusion

Food allergies are pervasive and potentially life threatening, but in general they can be linked to eight major food allergens. Generally, the larger the amount of allergen ingested, the greater the allergic reaction an individual has. DBPCFC remains the gold standard for diagnosing a food allergy. Because this is a laborious diagnostic tool, many people do not undergo accurate testing and falsely believe they are allergic when in fact they are not, and eliminate foods unnecessarily from their diet. Elimination and strict avoidance remain the mainstays for the treatment of food allergies. Because of our limited treatment options, strides have been made to improve labeling and preparation of foods, in order to avoid cross contamination. This is particularly true in the case of tree nuts and peanuts, which are difficult to distinguish. Emerging research in protein structures is helping to identify allergens that may be targeted in novel treatments for food-allergic individuals.

Cross-References

- ▶ Cow's Milk Allergy
- ▶ Delayed Anaphylaxis to Mammalian Meat (Alpha-Gal)

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- ▶ Diagnostic Components: Allergen for In Vivo (Skin Testing, Immunotherapy) and In Vitro (Serology) IgE Antibody Testing
- ▶ Diagnostic Food Challenges
- ▶ Egg Allergy
- ▶ Fatal Allergic Reactions to Foods
- ▶ Food Allergies, Diagnostic Testing
- ▶ Food Allergy and its Future Treatment
- ▶ Food Allergy, Overview
- ▶ Oral Allergy Syndrome
- ▶ Peanut Allergy

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Food Allergies, Diagnostic Testing

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Synonyms

Allergy skin prick testing; Component resolved diagnosis; Eosinophilic esophagitis; Epitope profiling; IgE-mediated food allergy; Non-IgE-mediated food allergy; Oral food challenges; Specific IgE immunoassay

Definition

Diagnostic evaluation for food allergy requires a multistep approach that integrates data from multiple sources including the clinical and dietary history, in vivo and in vitro allergy testing, and food challenges or elimination diets. Obtaining an accurate diagnosis is necessary to minimize the medical and psychosocial complications of food allergic disorders.

Introduction

Food allergy is a significant public health concern due to increasing prevalence and profound effects on medical, psychosocial, and economic functions of affected individuals and families. Current estimates suggest an overall food allergy prevalence (▶ Epidemiology of Food Allergy) of 3.9 % in children less than 18 years, representing an 18 % increase in prevalence from 1997 to 2007 (Branum and Lukacs 2009). Food-allergic individuals are at high risk for severe, life-threatening reactions (▶ Fatal Allergic Reactions to Foods) following allergen ingestion, and this risk, along with the significant dietary (▶ Allergen Avoidance: Dietary Management of Food Allergy) and social modifications required for allergen elimination, has adverse effects on quality of life (Burks et al. 2012). Obtaining an accurate diagnosis is critical to prevent unnecessary dietary elimination, provide for adequate nutrition (▶ Nutrition in Food Allergy) and appropriate psychological support, and minimize economic and psychosocial adversity for affected individuals and families. Further, data from a meta-analysis of studies evaluating the prevalence of food allergy (▶ Epidemiology of Food Allergy) suggest that up to 35 % of individuals with an adverse food reaction believe they have a food allergy, even though studies confirming food allergy by oral food challenge support a 10-fold lower prevalence of 3.5 % (Rona et al. 2007). Recent national guidelines for the diagnosis and management of food allergy defined food allergy (▶ Food Allergy, Overview) as an "adverse health effect arising from a specific immune response that occurs reproducibly on exposure to a given food," an inclusive definition that incorporates both IgE- and non-IgE-mediated food hypersensitivity (2010). Because no single testing modality is fully reliable for diagnostic testing for food allergy, these guidelines recommend a stepwise approach to diagnosis. In general, clinical diagnosis of food allergy synthesizes data obtained from the following sources: history and physical examination, skin prick testing (SPT) (▶ Methods (In Vivo): Skin Test (Intradermal, Puncture)), in vitro

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testing (▶ Single-Plex Immunoassays and Autoanalyzers), food challenges, elimination diets, food diaries, and, primarily in the case of non-IgE/ (▶ Allergic Proctocolitis and Food Protein-Induced Enterocolitis Syndrome (FPIES)) mixed IgE-non-IgE-mediated disorders such as eosinophilic esophagitis (EoE) (▶ Eosinophilic Gastrointestinal Disorders) and gastrointestinal endoscopy and biopsy.

Clinical History

A detailed clinical history and physical examination are critical first steps in the diagnosis of both IgE (▶ Food Allergy, Overview)- and non-IgE-mediated food allergy (▶ Allergic Proctocolitis and Food Protein-Induced Enterocolitis Syndrome (FPIES)), as the history informs and directs subsequent testing and interpretation of results. The clinical spectrum of food allergic disorders is listed in Table 1 (Burks et al. 2012). The clinical history should focus on the triggering food(s) and quantity ingested, symptoms elicited following ingestion of the triggering food(s), the timing and reproducibility of symptoms, the form of the food ingested (i.e., raw vs. baked), nature of reactions, and associated factors such as exercise, menses, illness, or concomitant ingestion of aspirin or alcohol (American College of Allergy Asthma and Immunology 2006). Reproducible symptoms will usually develop consistently after ingestion of an implicated food allergen; thus, the ability to tolerate standard servings of a food protein is important historical data that can exclude IgE-mediated food allergy. However, the clinician must consider that small, subthreshold quantities of a food allergen or extensively baked/heated foods can be ingested without reaction (Burks et al. 2012). Further, diagnosis in children is often challenging as they may not be able to articulate their specific symptoms and may present with food refusal, irritability, or other nonspecific symptoms. The majority of IgE-mediated food allergic reactions can be attributed to the "major food allergens" (▶ Food Allergens) such as milk (▶ Cow's Milk Allergy), egg (▶ Egg Allergy), soy, wheat, peanuts (▶ Peanut Allergy), tree nuts, fish, and shellfish; however, over 170 different food allergens have been identified, and the implicated allergens vary by geographic region (Sicherer and Sampson 2009; Burks et al. 2012).

Food Allergies, Diagnostic Testing, Table 1 Clinical spectrum of food allergic disorders (Modified from Burks et al. (2012))

IgE-mediated *Immediate/acute hypersensitivity*	Mixed IgE/non-IgE-mediated *Chronic/delayed onset*	Non-IgE-mediated *Cell mediated chronic/delayed onset*
Urticaria/angioedema	Atopic dermatitis	Food protein-induced enterocolitis syndrome (FPIES)
Anaphylaxis	Eosinophilic esophagitis	Food protein-induced allergic proctocolitis
Food-associated, exercise-induced anaphylaxis	Eosinophilic gastroenteritis	Heiner syndrome
Pollen-associated food allergy ("oral allergy syndrome")		Allergic contact dermatitis

Clinical symptoms associated with IgE-mediated "immediate" food allergy (▶ Food Allergy, Overview) generally present within minutes to 1–2 h following ingestion of the food allergen and can involve multiple systems including the skin (urticaria (▶ Urticaria), angioedema, erythema, pruritus), gastrointestinal tract (vomiting, abdominal pain, cramping), and respiratory tract (cough, wheezing, stridor, hoarseness, rhinorrhea, respiratory distress), as well as circulatory collapse, hypotension, and lethargy. In contrast, symptoms of non-IgE-mediated "cell-mediated" food allergy (▶ Allergic Proctocolitis and Food Protein-Induced Enterocolitis Syndrome (FPIES)) typically present several hours after ingestion of the food, and symptoms tend to be predominantly abdominal, including vomiting, diarrhea, bloody stools, or abdominal pain. Children with food allergy are at increased risk for other atopic disorders (▶ Diagnostic Terms: Atopy) such as asthma

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Food Allergies, Diagnostic Testing, Table 2 Differential diagnosis of food allergy (Modified from NIAID Guidelines (2010))

Allergic reactions due to nonfood allergens (e.g., aeroallergens, insect stings, antibiotics)
Gastroesophageal reflux
Lactose intolerance
Irritant effects of foods (e.g., hot or spicy foods)
Gustatory rhinitis or gustatory flushing
Toxin-induced food poisoning (e.g., scombroid)
Behavioral/mental disorders (e.g., anorexia nervosa, bulimia)
Pharmacologic effects of food chemicals or additives
Non-food allergen-triggered exacerbation of atopic dermatitis
Infections (for eosinophilic disorders, consider parasite infections)

(▶ Asthma variants: Allergic Asthma), atopic dermatitis/eczema (▶ Atopic Dermatitis), and allergic rhinitis; thus, the history should also evaluate for these comorbid clinical conditions (Branum and Lukacs 2009; Skripak et al. 2007; Sicherer et al. 2001; Skolnick et al. 2001). The differential diagnosis of food allergy is listed in Table 2 (2010).

Allergen-Specific IgE Testing/Skin Prick Testing

Although the medical history and clinical symptoms are critical in informing the diagnosis, neither the history nor physical examination alone is diagnostic of food allergy. For IgE-mediated food allergy, testing for allergen-specific IgE (sIgE) (▶ Specific IgE) to the foods implicated in the history is an important next step. Measurement of sIgE can be quantified by use of in vivo allergy skin prick tests (SPTs) (▶ Methods (In Vivo): Skin Test (Intradermal, Puncture)) and/or in vitro allergen immunoassays (▶ Methods (In Vitro and In Vivo): Multiplex Immunoassay Systems) (e.g., ImmunoCAP, CAP-FEIA system).

Epicutaneous SPT is commonly used in the evaluation of food allergy and is considered a safe procedure (Reid et al. 1993); however, it should be performed by allergy practitioners accustomed to the testing protocol and possessing the expertise to manage severe anaphylaxis in medical settings equipped with emergency medications and equipment. SPT is best utilized in patients with a suggestive clinical history to confirm food allergy or to exclude IgE-mediated allergy in patients without a suggestive clinical history. SPT is highly sensitive (Performance Measures: Diagnostic Sensitivity) (general estimates >90 %), but only modestly specific (▶ Predictive Value Model for Laboratory Tests: Diagnostic Sensitivity, Diagnostic Specificity, Positive and Negative Predictive Value, Efficiency, Likelihood Ratio ([positive and negative]), Incidence and Prevalence) (general estimates 50 %) depending on the extract utilized (American College of Allergy Asthma and Immunology 2006). The negative predictive value of SPT is high, with a negative skin test confirming the absence of an IgE-mediated reaction with 90–95 % accuracy. Because of an increased risk of adverse systemic reactions compared with SPT, intradermal skin tests are not recommended for diagnosis of food allergy (2010). Atopy patch tests (APTs) are also not routinely recommended for clinical diagnosis of food allergy, although there is some support for use of these tests for diagnosis of non-IgE-mediated and mixed disorders such as EoE in research settings.

When performing SPT (▶ Methods (In Vivo): Skin Test (Intradermal, Puncture)), the allergen, along with appropriate positive (histamine) and negative (saline) controls, is pricked through the first layer of skin using one of several commercially available applicator devices. Food allergen extracts for testing can be obtained from commercially available food extracts (prepared 1:10 or 1:20 weight/volume in glycerin) or from fresh food sources. After the food protein is pricked into the skin, if food-specific IgE is present on cutaneous mast cells, the cells will degranulate and release histamine and other mediators of immediate hypersensitivity that result in increased vascular permeability and localized cutaneous swelling resulting in a wheal (Analytes and Biomarkers: Wheal and Erythema:

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Skin Test Response). Vasodilatation also develops as a result of an axonal reflex resulting in a flare. The tests are read after approximately 15 min. An SPT that results in a wheal of at least 3 mm diameter after subtracting the saline control is considered positive (Eigenmann and Sampson 1998). SPT should be performed with caution in patients with high risk for severe anaphylaxis, including patients with poorly controlled asthma or those with severe atopic dermatitis or other skin conditions such as dermatographism, which could confound interpretation of the results. Many factors can affect skin test reactivity (Cox et al. 2008), including medications such as antihistamines, tricyclic antidepressants, or topical steroids that may inhibit the wheal and flare response in the skin, and as such, these medications should be discontinued prior to testing. Further, skin testing is generally not performed for several weeks after an episode of severe anaphylaxis.

Measurement of food-specific IgE by (▶ Specific IgE) immunoassay is another commonly utilized diagnostic tool (2010). Presently, commercially available tests utilize fluorescent enzyme immunoassay (FEIA) tests, although previous in vitro diagnostic tests utilized radioallergosorbent tests (RASTs), and this term continues to be used incorrectly in medical jargon. In contrast to SPT, IgE immunoassays tend to be more costly and less sensitive than SPT, depending on the food allergen, and the data are not as immediately available. This modality is useful for patients who are unable to discontinue antihistamines or other medications that could confound SPT results and is safe for high-risk patients or patients with, for example, severe atopic dermatitis for whom skin testing could exacerbate disease. Data from food-allergic children in the United States older than 2 years of age has established 95 % predictive levels for the major food allergens egg, milk, peanut, tree nuts, and fish, and these values are listed as follows: egg (▶ Egg Allergy) 7 kUA/L (2 kUA/L if <2 years), milk (▶ Cow's Milk Allergy) 15 kUA/L (5 kUA/L for children <2 years), peanut (▶ Peanut Allergy) 14 kUA/L, tree nuts approximately 15 kUA/L, and fish 20 kUA/L (Caubet and Sampson 2012). In a retrospective study of 604 food challenges in 391 children with food-specific IgE levels measured by CAP-RAST, for milk and egg, 50 % of children with levels of 2 kUA/L tolerated these foods on the challenge (Perry et al. 2004). Although cutoff values predicting the probability of clinical reactivity to specific foods have been established, the predictive value of these studies is not sufficiently high enough to obviate the need for oral food challenges. Further, quantification of food-specific IgE (PST or sIgE immunoassay) cannot differentiate asymptomatic sensitization from symptomatic clinical allergic reactions, due at least in part to the use of allergen extracts that may include a mixture of allergenic and nonallergenic constituent proteins, some of which could potentially cross-react with homologous proteins.

Oral Food Challenges

Oral food challenges (OFCs) (▶ Diagnostic Food Challenges) are considered the gold standard for the diagnosis of food allergy and are generally performed to either confirm a food allergy diagnosis at initial challenge or verify the ability of a patient to tolerate a food allergen and establish resolution of a food allergy (Nowak-Wegryzn et al. 2009; Jarvinen and Sicherer). Three types of food challenges (▶ Methods (In Vivo) Provocation Tests (Nasal Challenge, Bronchial Challenge, Food Challenge)) are utilized clinically – double-blind, placebo-controlled food challenges, single-blind challenges, and open food challenges. Double-blind placebo-controlled food challenges (DBPCFCs) have the benefit of removing both observer and patient bias in confirming the diagnosis; however, DBPCFCs are time-consuming and resource-intensive procedures. Therefore, single-blind or open food challenges are most helpful when no clinical symptoms are elicited and the challenge is negative and a diagnosis of food allergy can be ruled out. If objective symptoms are elicited during single-blind or open food challenges, then those symptoms should be correlated with the

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medical history and in vivo (SPT) or in vitro laboratory studies to confirm a diagnosis of food allergy. Because food challenges involve risk of potentially severe allergic reactions, challenges should be performed in a medical facility by experienced personnel, skilled in the management of anaphylaxis and shock. Further, patients should be carefully selected based on a number of variables such as age, severity of past reactions, comorbid diseases (e.g., uncontrolled asthma, severe atopic dermatitis), and current medication usage (Jarvinen and Sicherer; Nowak-Wegryzn et al. 2009). The general procedure for food challenges (▶ Methods (In Vivo) Provocation Tests (Nasal Challenge, Bronchial Challenge, Food Challenge)) involves strict dietary elimination of the food allergens of concern for a period of 2–8 weeks prior to challenge. Challenges are performed while the patient is on minimal or no symptomatic medications such as antihistamines. Incrementally increasing doses of the food allergen of interest are administered until a standard, age-appropriate serving size is tolerated, or symptoms are elicited indicating a positive challenge.

Food Elimination Diets

Non-IgE-mediated and mixed IgE/non-IgE-mediated disorders are often difficult to diagnose due to lack of reliable tests; food-specific IgE tests will be negative, and therefore diagnosis relies heavily on the clinical history, possibly food challenges, and elimination diets. Thus, elimination of specific foods from the diet may be most helpful in the diagnosis of non-IgE-mediated (e.g., FPIES, allergic proctocolitis (▶ Allergic Proctocolitis and Food Protein-Induced Enterocolitis Syndrome (FPIES)) and mixed IgE/non-IgE-mediated food allergic disorders (e.g., EoE) (2010). Resolution of symptoms following elimination of the suspected food allergen coupled with a supportive history lends support to the diagnosis of food allergy. However, careful attention to nutritional status and appropriate nutritional support (▶ Nutrition in Food Allergy) should be provided to minimize the risk of nutritional deficiencies, and trial elimination diets should be of limited duration. The spectrum of elimination diets can include restriction of one or more specific foods from a patient's diet to use of a complete "elemental" diet consisting of only extensively hydrolyzed or amino acid-based formulas. Food diaries are sometimes utilized to document everything that a patient consumes and generally most helpful when the history is complex, when hidden food ingredients are identified, or in identifying patterns of reactions in association with exercise, illness, menses, or alcohol consumption.

New Approaches to Food Allergy Diagnosis

Functional Assays

Basophils are (▶ Basophils) key cellular effectors of allergic disease. Their utility as a diagnostic tool for IgE-mediated food allergy lies in the ability to measure their biologic response during ex vivo stimulation. Basophil histamine release (BHR) assays measure histamine release from blood basophils that are stimulated with food allergen proteins. BHR has poor sensitivity and specificity and does not provide any additional information that cannot be obtained with standard measurements of sIgE, such as SPT (Hamilton and Franklin 2004). The basophil activation test (BAT) involves direct basophil activation with antigen with subsequent measurement of up-regulation of cell surface proteins that are associated with release of basophil mediators. Although still primarily a research tool, the BAT has shown promise in refining the ability to predict clinical milk allergy (Wanich et al. 2009; Rubio et al. 2011) and predict challenge outcomes in children with egg or milk allergy (Sato et al. 2011). Further studies are necessary, but it is possible that the BAT could enhance clinical knowledge regarding patient's sensitization profiles, particularly when used with recombinant proteins (Caubet and Sampson 2012).

Molecular Diagnosis of Food Allergy

Advances in molecular and proteomic techniques have led to development of novel approaches to

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food allergy diagnostics including component-resolved diagnostics (CRD) and epitope profiling (Caubet and Sampson 2012). CRD has been shown to enhance specificity and help differentiate cross-reactivity and sensitization by examining specific immune responses at the level of individual recombinant purified proteins. Allergen epitope profiling evaluates the specific IgE-binding epitopes using peptide microarray-based immunoassays. This technique has shown promise in recent studies demonstrating associations between allergen severity/clinical phenotype and IgE epitope diversity and affinity.

Unproven Diagnostic Techniques

Recommendations from the United States NIAID Expert Panel Report do not support the use of the following nonvalidated tests for clinical diagnosis of food allergy, including facial thermography, lymphocyte stimulation, gastric juice analysis, endoscopic allergen provocation, hair analysis, applied kinesiology, provocation-neutralization, cytotoxic assays, electrodermal test (Vega), and mediator release assay (LEAP diet) (2010). Basophil histamine release/activation is often used in research studies as an evaluation of basophil mediator release, but is not standardized for routine clinical practice. Serum food-specific IgG4 has also been utilized to screen for food allergy and often results in multiple positive results, which represent a normal immune response to foods, and is not predictive of food allergy (Stapel et al. 2008). From a research standpoint, serum IgG4 may play a protective role as a blocking antibody and has been associated with tolerance development both clinically (Lemon-Mule et al. 2008; Caubet et al. 2012; Savilahti et al. 2010) and during investigative oral immunotherapy trials (▶ Food Allergy and its Future Treatment) (Jones et al. 2009; Skripak et al. 2008).

Conclusions

Obtaining an accurate diagnosis of food allergy is vital to prevent unnecessary dietary restriction, as well as to mitigate the psychosocial and economic complications of this disorder. A multistep approach to diagnosis of food allergy, integrating data from the clinical history and physical examination with specific in vivo and in vitro laboratory studies and/or diagnostic food challenges, enhances diagnostic accuracy (Table 3). New approaches to food allergy diagnostics including CRD and epitope mapping will likely further enhance the specificity and sensitivity of existing tests and provide accurate, viable markers of clinical sensitivity to enhance the care of patients with allergic disease. Further studies are needed to develop biomarkers for non-IgE-mediated food allergy and improve diagnostic accuracy for this complex collection of disorders.

Food Allergies, Diagnostic Testing, Table 3 Clinical pearls

Diagnosis of food allergy requires integration of data from multiple sources including the clinical history, physical examination, allergy skin prick testing, IgE immunoassay, and/or food challenges
Interpretation of allergy testing results should always be done in the context of the clinical history as current diagnostic tests cannot differentiate asymptomatic sensitization from clinical reactivity
The ability of an individual to consume a food protein in his/her diet without reaction is excellent historic evidence to exclude food allergy
Oral food challenges are considered the current "gold standard" for food allergy diagnosis
Multiple unproven diagnostic methods exist and should be avoided
New molecular approaches to food allergy diagnosis are under investigation

Cross-References

- ▶ Allergen Avoidance: Dietary Management of Food Allergy
- ▶ Allergic Proctocolitis and Food Protein-Induced Enterocolitis Syndrome (FPIES)
- ▶ Asthma Variants: Allergic Asthma
- ▶ Atopic Dermatitis
- ▶ Basophils
- ▶ Cow's Milk Allergy

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- ▶ Diagnostic Food Challenges
- ▶ Diagnostic Terms: Atopy
- ▶ Egg Allergy
- ▶ Eosinophilic Gastrointestinal Disorders
- ▶ Epidemiology of Food Allergy
- ▶ Fatal Allergic Reactions to Foods
- ▶ Food Allergens
- ▶ Food Allergy and its Future Treatment
- ▶ Food Allergy, Overview
- ▶ Methods (In Vitro and In Vivo): Multiplex Immunoassay Systems
- ▶ Methods (In Vivo) Provocation Tests (Nasal Challenge, Bronchial Challenge, Food Challenge)
- ▶ Methods (In Vivo): Skin Test (Intradermal, Puncture)
- ▶ Nutrition in Food Allergy
- ▶ Peanut Allergy
- ▶ Specific IgE
- ▶ Urticaria

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Food Allergy and its Future Treatment

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Synonyms

Epicutaneous immunotherapy (EPIT); Oral immunotherapy (OIT); Sublingual immunotherapy (SLIT)

Definition

Future treatments for food allergy are defined as novel therapies currently under investigation and are not approved by the Food and Drug Administration (FDA) for clinical use. These include both allergen-specific and non-allergen-specific approaches.

Introduction

Food allergies are a growing problem in developed countries. Over the past two decades, the prevalence in children has increased nearly 20 %, and during the same time period allergy to peanut has tripled (Boyce et al. 2010). Food allergies result in over 300,000 ambulatory care visits annually and nearly $500 million in both direct and indirect health-care costs per year (Boyce et al. 2010). An estimated 150–200 people die each year due to food-related anaphylaxis (Bock et al. 2001).

Although the prevalence is increasing, treatment options for food allergy remain limited (Boyce et al. 2010). Current management strategies include strict dietary avoidance of offending foods, nutritional counseling, and emergency treatment of adverse reactions. These treatment options are complicated by problems with reading/understanding food labels, difficulty in adhering to a food elimination diet, the frequent threat of accidental ingestions, and the risk of severe or even fatal food reactions.

Primary prevention strategies to reduce the prevalence of food allergy have not been successful. The United Kingdom Committee on Toxicity (COT) and the American Academy of Pediatrics (AAP) have both published guidelines for the prevention of food allergies, but these recommendations have not averted the development of atopic diseases such as asthma, eczema, or food allergy through strategies targeting the timing or diversity of food introduction in infancy and early childhood (Greer et al. 2008).

A number of novel therapies are currently under investigation that may provide new avenues for food allergy treatment (Table 1).

Desensitization Versus Tolerance

The goals of immunomodulatory therapy for food allergy include induction of both clinical desensitization and long-term immune tolerance. "Desensitization" is a change in the

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Food Allergy and its Future Treatment, Table 1 Novel therapies for food allergy

Allergen specific	
Subcutaneous immunotherapy (SCIT)	High number of systemic reactions in treatment of food allergy
Epicutaneous immunotherapy (EPIT)	Improved tolerance to milk compared to placebo, but higher incidence of side effects. Currently under investigation in peanut allergy
Sublingual immunotherapy (SLIT)	Fewer systemic side effects than SCIT or OIT but less benefit in inducing desensitization/tolerance
Oral immunotherapy (OIT)	75–100 % of patients will achieve desensitization, but long-term tolerance has not been documented. Higher frequency of systemic side effects than SLIT
Extensively heated foods	Up to 80 % of milk-/egg-allergic patients can ingest extensively heated milk/egg products. Uncertainty remains over degree of heating required and is not applicable for all foods
Modified food allergens	Methods that allow stimulation of the immune system to induce tolerance with a reduced risk of anaphylaxis in animal studies
Allergen nonspecific	
Chinese herbal therapy	Minimal side effects and appears to induce long-term tolerance after cessation of use. Early clinical studies are in progress
Anti-IgE	Improves threshold consumption of food allergens but has higher risk of anaphylaxis. A subset of patients have no benefit
Anti-IL-5	Effective at reducing eosinophil number and clinical symptoms in EoE, but long-term effectiveness and safety data are needed
Probiotics/ Prebiotics	May reduce risk of developing atopic disease, but no clear benefit in treating food allergy to date
Trichuris suis ova	May protect against development of IgE sensitization to foods, but no human studies are available to date
Modified *Lactococcus lactis*	In animal models, reduces the risk of anaphylaxis during food challenge and promotes shift from Th2 to Th1 cytokine production
TLR-9 agonists	In an animal model, protected against peanut induced anaphylaxis, but no human studies are available to date

threshold dose of food allergen necessary to induce an allergic reaction which requires continuous allergen exposure. If exposure is stopped, the state of desensitization ceases and the risk of reaction upon future allergen exposure is high. "Tolerance" involves the induction of long-term immune changes that allow for ingestion of a food allergen without reaction and does not require continuous allergen exposure. Desensitization can often be induced in a relatively short amount of time while development of tolerance requires a much longer time period.

Allergen-Specific Treatments

Allergen-specific treatment modalities provide a targeted approach by directing therapy against a specific food allergen. These treatments do not typically provide a broad impact upon multiple food allergens.

Subcutaneous Immunotherapy

Subcutaneous immunotherapy (SCIT) is traditionally used and highly effective for the treatment of seasonal/perennial allergic rhinoconjunctivitis and venom hypersensitivity. Attempts to utilize SCIT to treat food allergy date back to the 1930s. SCIT has been shown to be effective at increasing desensitization after peanut ingestion, but it has been complicated by a high number of systemic reactions (Nowak-Wegrzyn and Sampson 2011). SCIT has thus been abandoned as a treatment modality for food allergy. SCIT to pollens is effective in reducing oral symptoms and skin reactivity in patients with pollen food allergy syndrome (PFAS) (Asero 1998). Symptoms associated with PFAS occur typically after ingestion of raw fruits and vegetables in patients with seasonal allergies; reactions are due to cross-reactivity between the offending environmental allergen (e.g., birch pollen) and foods (e.g., apples, cherries, and carrots), but reactions are typically limited to the oropharynx.

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Epicutaneous Immunotherapy

Epicutaneous immunotherapy (EPIT) involves the presentation of allergen through direct contact with the skin. After exposure, the allergen is recognized by antigen-presenting cells (APCs) and presented to T cells in regional lymph nodes, allowing for generation of a specific T cell immune response (Dioszeghy et al. 2009). EPIT is effective in the treatment of seasonal allergies and has also been studied in the treatment of food allergy. In a mouse model, EPIT was as effective as SCIT in reducing airway hyperresponsiveness and reactivity to peanut (Mondoulet et al. 2011). Children (ages 3 months to 15 years) treated with EPIT were able to consume more milk protein during an oral food challenge performed after 3 months on EPIT compared with the placebo group; however, more side effects were noted in the EPIT-treated group (Dupont et al. 2010). Studies are currently underway to investigate EPIT for the treatment of peanut allergy.

Sublingual Immunotherapy

Sublingual immunotherapy (SLIT) involves placing gradually increasing doses of a liquid allergen concentrate under the tongue to achieve a target maintenance dose after months of therapy. SLIT is effective in the treatment of aeroallergen sensitivity and has several advantages over traditional SCIT. There are fewer side effects and it can frequently be dosed at home, which is likely to improve patient adherence.

SLIT has been used successfully for several foods including kiwi, hazelnut, peach, milk, and most recently peanut (Nowak-Wegrzyn and Sampson 2011). In a study of peanut-allergic patients, SLIT-treated subjects were able to consume more peanut protein during oral food challenge and developed immunologic changes suggesting desensitization (Kim et al. 2011). Side effects were infrequent, and symptoms were typically limited to the oropharynx. In another trial comparing SLIT versus SLIT plus oral immunotherapy for milk allergy, SLIT was associated with lower side effect profiles but with more modest changes in threshold doses of milk allergen consumption (Keet et al. 2012).

Oral Immunotherapy

Oral immunotherapy (OIT) represents the area of most active research in food allergy treatment (Nowak-Wegrzyn and Sampson 2011). OIT typically involves several phases. The initial treatment phase, modified rush desensitization, involves giving 6–8 incremental doses of the food allergen in rapid succession on the first day. This initial phase is then followed by a buildup phase during which the patient ingests a daily dose of the allergen with dose escalations every 1–2 weeks until a target dose is reached over months of therapy. The maintenance phase involves regular, daily ingestion of a consistent dose of allergen for a scheduled amount of time, typically years. After these phases, patients typically undergo an oral food challenge to evaluate for development of desensitization and/or tolerance.

OIT trials to date have been conducted in patients with allergies to milk (Keet et al. 2012; Longo et al. 2008; Skripak et al. 2008), egg (Buchanan et al. 2007; Jones et al. 2010), and peanut (Blumchen et al. 2010; Varshney et al. 2011). In general, 50–90 % of patients will reach a state of desensitization within 1–2 years of treatment. While there has been some evidence of short-term tolerance in a small subset of subjects, there has been no documentation of long-term tolerance using OIT (Jones et al. 2010). Side effects are frequent with OIT, although the majority are mild to moderate and limited to the oropharynx. More serious side effects such as vomiting, urticaria/angioedema, laryngeal edema, or respiratory distress have occurred, and nearly 20 % of all patients treated with OIT will have significant gastrointestinal side effects that prevent future treatment (Nowak-Wegrzyn and Sampson 2011).

When comparing OIT to SLIT, several differences are noticed. SLIT has fewer systemic side effects, with the potential for home dosing and improved compliance, while OIT allows for larger doses and induces more immunologic changes with a greater chance of desensitization and tolerance induction.

OIT has also been combined with an anti-IgE treatment, omalizumab (Xolair®), to improve

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safety and reduce time to maintenance dosing. In a study of 11 milk-allergic patients, treatment with both milk OIT and omalizumab was associated with fewer side effects than as reported previously with OIT alone, and this approach allowed patients to reach maintenance dosing faster than with OIT alone (Nadeau et al. 2011).

Although OIT is effective at achieving desensitization for a variety of food allergens, more work is needed to improve safety, to understand the immunologic mechanisms involved, and to assess the ability to induce tolerance before OIT becomes a mainstream treatment modality.

Extensively Heated Foods

All allergens contain epitopes, areas of the protein structure recognized and bound by the immune system. Certain foods, such as milk and egg, contain conformational epitopes that are created through the folding of the protein. Heating of these foods can lead to disruption of the conformational epitopes and decreased recognition by the immune system.

Up to 80 % of egg- and milk-allergic patients can safely ingest extensively heated egg and milk products (Lemon-Mule et al. 2008; Nowak-Wegrzyn et al. 2008). Therapy with extensively heated foods has been associated with decreased immune activation and a shorter time to tolerance induction when compared to diet restriction alone. Despite these benefits, ingestion of extensively heated foods can still be problematic. Neither skin prick nor specific IgE testing accurately identifies which patients can tolerate extensively heated foods; thus, an oral food challenge is often required before these foods can be added to the diet. There is also uncertainty about the degree of heating required to prevent a reaction. Extensive heating does not reduce allergenicity in all foods. Foods such as peanut contain linear epitopes that do not depend upon protein folding and are resistant to the effects of heating.

Modified Food Allergens

Advances in molecular technology have allowed for direct modification of allergens using recombinant techniques. This process may allow for stimulation of the immune system and induction of tolerance while minimizing the risk of anaphylaxis.

One example uses heat-killed *Listeria monocytogenes* (HKL) and heat-killed *E. coli* (HKE) combined with recombinant allergens. In an animal model of peanut allergy, HKL was used as an adjuvant with modified peanut proteins and led to a reduction in clinical symptoms and risk of anaphylaxis upon exposure to peanut (Li et al. 2003). A phase 1 clinical trial is currently underway to evaluate this treatment in humans.

Another example of using modified food allergens is peptide immunotherapy. This form of treatment utilizes small fragments of a protein, called a peptide, rather than the whole allergen. These fragments are generally too small to activate mast cells or basophils, two cells associated with generation of the allergic response. Since these cells are not activated, the risk of anaphylaxis should be significantly reduced. Peptide immunotherapy has been studied previously in both cat and bee venom allergy but has a limited role in the treatment of food allergy, as many of the major food allergen epitopes remain to be defined. In animal models, peptide immunotherapy protected against anaphylaxis after ovalbumin challenge (Nowak-Wegrzyn and Sampson 2011). In a similar model, egg peptides given orally led to a reduction in clinical symptoms after oral challenge with immune changes suggesting desensitization. Currently, there are no ongoing human trials using peptide immunotherapy.

Plasmid DNA immunotherapy has also been studied. This method allows direct delivery of allergen genes through plasmid DNA (pDNA) with generation of a specific immunomodulatory response. In an animal model of peanut allergy, pDNA containing peanut allergen was complexed with chitosan, a naturally occurring polysaccharide. During peanut challenge, mice treated with the pDNA/chitosan had lower anaphylaxis scores and decreased histamine levels compared to placebo (Nowak-Wegrzyn and Sampson 2011). In another study, pDNA containing transforming growth factor beta

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(TGF-β) was complexed with chitosan and led to decreased IgE, increased Th1 cytokine production, and tolerance to ovalbumin after challenge.

Other modalities studied include use of synthetic immunostimulatory oligodeoxynucleotides containing unmethylated CpG motifs (ISSs) that can be linked to allergens, human immunoglobulin Fc-Fc fusion proteins, and conjugation of mannoside, a polysaccharide, with food allergens (Nowak-Wegrzyn and Sampson 2011). All of these have shown promise in reducing the risk of anaphylaxis or immune changes suggesting desensitization but require further investigation in both animal models and in humans before they can be used clinically.

Allergen-Nonspecific Treatments

Allergen-nonspecific therapies are not targeted toward a specific allergen but rather the overall immune response. The benefit of this approach is the potential for a more global impact on the allergic response than when utilizing single allergen-specific approaches.

Chinese Herbal Therapy

Chinese herbal remedies have been used for centuries to treat a variety of medical conditions. Recently, work has begun using these compounds in the treatment of food allergy. In a mouse model of peanut allergy, an 11-herb mixture known as food allergy herbal formula (FAHF-1) protected against peanut-induced anaphylaxis after challenge, associated with a reduction in host Th2 cytokine production (Li and Brown 2009). A newer 9-herb formula (FAHF-2) has been evaluated in humans (Wang et al. 2010). Initial studies in peanut-allergic mice treated with FAHF-2 showed tolerance induction to peanuts for up to 6 months, associated with a reduction in Th2 cytokines and other markers of immune activation. A phase 2 clinical trial is currently ongoing.

Anti-IgE

IgE is the predominant molecule responsible for the recognition of food allergens by the immune system. IgE binds to food allergens and subsequently activates mast cells and basophils leading to release of mediators such as histamine and the generation of inflammatory cytokines resulting in the constellation of clinical symptoms associated with allergic reactions (Boyce et al. 2010). Anti-IgE molecules function by binding free IgE, which prevents binding to the IgE receptor and decreases activation of mast cells and basophils. Anti-IgE molecules have been effective in the treatment of allergic asthma. There have been two clinical trials of anti-IgE molecules in the treatment of food allergy. In the first trial, Hu-901 was studied in the treatment of peanut allergy. An increased threshold peanut dose during food challenge was noted in the group receiving treatment; however, high doses of the medication were required and nearly a quarter of patients studied had no benefit (Nowak-Wegrzyn and Sampson 2011). In the second trial, omalizumab was also studied in peanut-allergic patients. Although those receiving omalizumab tolerated increased peanut protein doses during challenge, two patients developed severe anaphylaxis leading to termination of the study (Sampson et al. 2011). Currently, studies are underway to examine the use of anti-IgE as monotherapy, as well as its use in combination with OIT.

Anti-Interleukin-5 (IL-5)

Eosinophils play an important role in allergic diseases, in particular eosinophilic gastrointestinal disorders, such as eosinophilic esophagitis (EoE). EoE is a disorder characterized by infiltration of the esophagus by eosinophils leading to symptoms of vomiting, reflux, dysphagia, food impaction, and even esophageal strictures (Liacouras et al. 2011). The eosinophilic infiltrate is often a food antigen-driven process, and disease remission is associated with elemental or elimination diets. IL-5 is a prominent cytokine in the disease pathogenesis of EoE and has been a target for therapy. In a study by Straumann et al., mepolizumab, an anti-IL-5 molecule, led to a significant reduction in esophageal eosinophils compared to placebo; however, less than

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10 % of patients had a complete response (Straumann et al. 2010). Studies of reslizumab, another anti-IL-5 molecule, have also shown a dose-dependent reduction in esophageal eosinophils as well as a reduction in clinical symptoms (Spergel et al. 2005). Long-term remission and safety with these medications is still largely unknown in both children and adults and further investigation is needed.

Pro-/Prebiotics

Probiotics are living microorganisms that are part of the gastrointestinal microbiome and confer benefit to the host (Ozdemir 2010). Most probiotics arise from dairy products and contain *Lactobacillus* and *Bifidobacterium* species. Probiotics have been studied for a variety of gastrointestinal diseases including food allergy. In animal models of food allergy, probiotics reduce Th2 cytokine expression and promote oral tolerance. In a study of pregnant women treated with probiotics during pregnancy and 6 months postnatally, treated infants had less eczema than the placebo group, although there was no change in serum IgE or sensitization to foods (Nowak-Wegrzyn and Sampson 2011). Follow-up studies have been unable to reproduce these results, however. In a study of milk-allergic children, probiotics had no effect on induction of tolerance to cow's milk (Nowak-Wegrzyn and Sampson 2011).

Prebiotics are oligosaccharides that help promote probiotic colonization of the gastrointestinal tract. In a study of infants treated with prebiotics, the treatment group had a lower risk of atopy, recurring wheezing, and allergic urticaria compared to controls (Nowak-Wegrzyn and Sampson 2011). Additional investigation is needed of pro- and prebiotics before widespread use for atopic diseases can be recommended.

Trichuris suis Ova

Parasitic infections are known to disrupt Th1-Th2 balance; thus, these organisms may be useful treatment options to modulate the immune response associated with other diseases. Use of parasites as therapy has been effective in several diseases mediated by an imbalance of Th2 and Th1 cytokines such as ulcerative colitis, Crohn's disease, and multiple sclerosis. Although *Trichuris suis* was not effective in the treatment of grass pollen-induced rhinitis, studies in a mouse model suggest that it may be effective in protecting against food allergen sensitization (Nowak-Wegrzyn and Sampson 2011).

Modified *Lactococcus lactis*

Lactococcus lactis, formerly known as *Streptococcus lactis*, is used in the production of buttermilk and cheese. In a mouse model of food allergy, it has been modified to secrete IL-10, a cytokine important in the induction of tolerance. In mice treated with modified *Lactococcus lactis*, a decrease in beta-lactoglobulin IgE and anaphylaxis severity was noted (Nowak-Wegrzyn and Sampson 2011). *Lactococcus lactis* has also been modified to secrete IL-12 which led to the prevention of allergic reactions, decreased Th2 cytokines, and increased interferon-gamma, a Th1 cytokine, in a mouse model of food allergy (Nowak-Wegrzyn and Sampson 2011).

TLR-9 Agonists

Toll-like receptors (TLRs) play an important role in the innate immune response. Signaling through these receptors promotes generation of inflammatory cytokines. TLR-9, specifically, promotes downstream release of Th1 cytokines such as interferon-gamma. In a mouse model of food allergy, oral administration of a TLR-9 agonist provided protection against peanut-induced anaphylaxis (Nowak-Wegrzyn and Sampson 2011).

Conclusion

While current therapies for food allergies remain limited, a variety of novel therapies are under investigation and may provide future therapeutic alternatives (Table 2). For all of these emerging therapies, further investigation is needed to understand the underlying immune mechanisms to provide safe and effective treatment for food allergy.

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Food Allergy and its Future Treatment, Table 2 Clinical pearls

Current treatment of food allergy includes dietary avoidance, nutritional counseling, and emergency treatment of adverse reactions
A variety of novel therapies are under investigation for the treatment of food allergy with the goal of inducing long-term tolerance to offending foods
Approaches include allergen-specific and non-allergen-specific therapies
Several therapies are capable of inducing desensitization, but long-term tolerance has not yet been documented
Further investigation is needed to ensure patient safety

Cross-References

- Cow's Milk Allergy
- Diagnostic Components: Allergen for In Vivo (Skin Testing, Immunotherapy) and In Vitro (Serology) IgE Antibody Testing
- Diagnostic Components: T Helper Cell Cytokines (IL-4, IL-5, IL-9, IL-10, IL-13, IL-17)
- Diagnostic Food Challenges
- Egg Allergy
- Eosinophilic Esophagitis
- Eosinophilic Gastrointestinal Disorders
- Eosinophils in Disease
- Epidemiology of Food Allergy
- Fatal Allergic Reactions to Foods
- Food Allergens
- Food Allergies, Diagnostic Testing
- Food Allergy, Overview
- Food Desensitization
- Herbal Remedies
- IgE Testing
- Immunotherapy, Mechanisms
- mAbs (Omalizumab)
- Mast Cell Mediators
- Methods (In Vivo) Provocation Tests (Nasal Challenge, Bronchial Challenge, Food Challenge)
- Methods (In Vivo): Skin Test (Intradermal, Puncture)
- Nutrition in Food Allergy
- Oral Allergy Syndrome
- Peanut Allergy
- Role of IgE in Disease
- Role of Mast Cells in Diseases
- Single-Plex Immunoassays and Autoanalyzers
- Specific IgE

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Food Allergy, Overview

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Synonyms

Food hypersensitivity; Food-induced anaphylaxis

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Definition

Food allergy: An adverse health effect arising from a specific immune response that occurs reproducibly on exposure to a given food (Boyce et al. 2010).

Introduction

Food allergies affect millions of individuals worldwide, and their prevalence appears to be increasing, making this an important public health problem. Presentation of disease varies and may even be life threatening. Included in this entry is a brief overview of the prevalence, pathogenesis, and presentation of food allergy.

Food Intolerance Versus Food Allergy

The term *allergy* implies the involvement of an immune-mediated mechanism in eliciting an adverse health effect. By contrast, a non-immunologic mechanism leading to a reaction following food ingestion is termed *food intolerance*. An intolerance may be due to a metabolic (e.g., lactose intolerance or galactosemia), pharmacologic (e.g., alcohol or caffeine ingestion), toxin-mediated (e.g., bacterial food poisoning), or idiopathic/undefined (e.g., sulfite sensitivity) response. A more complete list of food intolerances is listed in Table 1.

Food allergy is the result of an immune-mediated response occurring after food exposure and may be classified based on the type of immune-mediated allergic response. Typically, reactions are categorized within one of three categories based on the immune mechanism(s) involved: (1) IgE mediated, (2) non-IgE mediated, and (3) mixed IgE and non-IgE mediated (Table 2). The following sections and entries will further elaborate on the distinctions between these groups and the diseases within their classifications.

Epidemiology and Prevalence of Food Allergy

According to the NIAID (National Institute of Allergy and Infectious Disease) guidelines on the Diagnosis and Treatment of Food Allergy (Boyce et al. 2010), between 1–2 % and 10 % of the population may have a food allergy, and estimates have stated as many as 1 in 13 children in the United States have a food allergy equaling approximately 5.9 million affected children (Gupta et al. 2011). Cumulative data from several national health surveys indicated an 18 % increase in the prevalence of food allergy between 1997 and 2007 in children less than 18 years old (Branum and Lukacs 2008). In addition, multiple other studies have reported increases in the prevalence of food allergy (Sicherer 2011), but because of numerous methodological limitations, it is difficult to draw firm conclusions with regard to the exact prevalence of food allergy.

It is important to note that while more than 170 foods have been reported to cause food allergy, only eight major foods or food groups cause the

Food Allergy, Overview, Table 1 Food intolerances (Metcalfe et al. 2008; Boyce et al. 2010)

Metabolic	Pharmacologic	Toxic	Idiopathic/undefined
Lactose intolerance	Caffeine ingestion	Scombroid fish poisoning[a]	Sulfite sensitivity
Galactosemia	Alcohol ingestion	Bacterial food poisoning	Anorexia nervosa
Pancreatic insufficiency	Histamine ingestion	Heavy metals poisoning	Auriculotemporal syndrome
Gallbladder disease	Tyramine ingestion		
Liver disease	Capsaicin ingestion		

[a]Scombroid fish poisoning results from histamine accumulation in improperly stored fish. Because the symptoms result from histamine ingestion, this may also be classified as a pharmacologic intolerance

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Food Allergy, Overview, Table 2 Food allergies (Sampson 2003; Metcalfe et al. 2008)

IgE mediated	Non-IgE mediated	Mixed IgE/Non-IgE
Acute urticaria	Celiac disease	Eosinophilic esophagitis
Acute angioedema	Dermatitis herpetiformis	Eosinophilic gastroenteritis
Oral allergy syndrome	Food-induced pulmonary hemosiderosis (Heiner's syndrome)	Atopic dermatitis
Gastrointestinal anaphylaxis	Food protein-induced enteropathy	
Generalized anaphylaxis	Food protein-induced proctocolitis	
Food-dependent exercise induced anaphylaxis	Food protein induced enterocolitis syndrome (FPIES)	
Acute bronchospasm (wheezing)	Allergic contact dermatitis	

majority of symptoms in the United States. Foods most commonly implicated in the United States include cow's milk, hen's egg, peanut, tree nuts (e.g., walnut, cashew, and pecan), wheat, soy, fish, and shellfish. Because of adverse effects on health-related quality of life, lack of a cure, and limitations on social interaction due to the ubiquitous nature of food, food allergy is a significant health concern (chapter by Thyagarajan).

Failure of Oral Tolerance Leads to Food Allergy

Failure of *oral tolerance* results in an allergic response leading to symptoms of food allergy. Upon ingestion, digestion begins and food proteins are introduced to the gastrointestinal mucosa. Food antigens may be taken up directly by dendritic cells, absorbed through M cells, or taken through intestinal epithelial cells. Antigen is most often presented by dendritic cells, which orchestrate the ensuing immune response. In a nonallergic individual, the immune response is suppressed by the action of regulatory T cells. Regulatory T cells, characterized as being CD4+ CD25+ and possessing the transcription factor FOX P3, are producers of regulatory cytokines, IL-10 and TGF-beta, which suppress Th1 and Th2 polarization. Allergic individuals, on the other hand, have activation of Th2 cells, characterized by cytokines IL-4, IL-5, and IL-13, which influence B cell production of specific IgE. Upon exposure to an antigen to which an individual is sensitized, specific IgE bound to mast cells is cross-linked, triggering the release of inflammatory mediators such as histamine, leukotrienes, and prostaglandins, leading to symptoms of an allergic reaction.

Prevention of Food Allergy

Currently there is no uniformly accepted recommendation for preventing food allergy. Common concerns include the effect of maternal diet during pregnancy and lactation and the timing of solid food introduction into the developing infant's diet. Interventional studies aimed at preventing food allergy are currently ongoing. The leading hypotheses aim toward understanding the importance of the timing of complementary food introduction and its role in the development of food allergy.

In 2000, the American Academy of Pediatrics (AAP), Committee on Nutrition, recommended delayed introduction of the most commonly allergenic foods based on few studies showing reduction in food-associated atopic dermatitis, urticaria, and gastrointestinal disease by 12 months (American Academy of Pediatrics 2000). Multiple studies since this time have suggested that delayed introduction may contribute to the development of food allergy, and evidence has been contradictory regarding a protective effect against development of other allergic diseases. In light of the newer evidence,

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in 2008 the AAP released a statement that complementary foods may be introduced between 4 and 6 months of age, and during this same time period, potentially allergenic foods may be introduced as well (Greer et al. 2008). Interventional studies in high-risk populations powered to directly answer the questions regarding the effect of allergenic food introduction on the development of food allergy are underway and have not been completed at the time of this publication.

Regarding the role of maternal diet during pregnancy and lactation, sufficient evidence does not exist to suggest that maternal diet during pregnancy or lactation affects the development or clinical course of food allergy. Results from a systematic review of the literature did not suggest that maternal dietary antigen avoidance during pregnancy or lactation had a protective effect on the incidence of atopic eczema in the first 18 months of life (Kramer and Kakuma 2006). Restrictive diets during pregnancy or lactation may adversely affect maternal or fetal nutrition and are not recommended.

IgE-Mediated Food Allergy

IgE-mediated reactions to food are the most widely known food-induced allergic reactions and may be life threatening. Examples of IgE-mediated reactions include acute urticaria and/or angioedema, flushing, pruritus, acute onset of wheezing or bronchospasm, oral allergy syndrome, food- and exercise-induced anaphylaxis, and generalized anaphylaxis (Metcalfe et al. 2008). Reactions are characterized by having a sudden onset, and typically symptoms develop within minutes to 2 h. Rarely, an IgE-mediated reaction may present with symptoms more than 2 h after ingestion (chapter by Yamini Virkud). An IgE-mediated reaction occurs when specific IgE bound to mast cells or basophils is cross-linked by the food-specific antigen and leads to release of preformed inflammatory mediators. Mast cell activation leads to release of histamine, prostaglandins, proteases, and the synthesis of lipid mediators and cytokines. Symptoms may present in any organ system, but are characteristically seen at the sites where mast cells are typically found – in tissues of the respiratory tract, gastrointestinal tract, cardiovascular system, and skin. Commonly, multiple organ systems are involved, and evidence has not substantiated a role for food allergy in chronic conditions such as asthma, chronic urticaria, and allergic rhinitis.

A double-blind, placebo-controlled food challenge is the gold standard for diagnosis of food allergy. More commonly, clinicians rely on serum-specific IgE testing, skin prick tests, and observed open oral food challenges when necessary (chapter by Amy Scurlock). In vitro quantification of specific IgE has been used by investigators to determine the likelihood of having an allergic reaction (Sampson 2001). Skin prick tests (SPT) are commonly used by allergists. This method involves using a needle, bifurcated needle, probe, or lancet to puncture the epidermis through an extract of a food (Metcalfe et al. 2008). Negative results have a greater than 95 % NPV. Positive and negative results must be interpreted in light of the historical reaction, with the predictive value waning if used in an unselected population. A positive skin test (a wheal measured 3 mm larger than the negative control) has a PPV of only approximately 50 %, though investigators have shown the larger the wheal diameter, the greater the PPV of the test for some foods (Hill et al. 2004). An oral food challenge may be necessary in some circumstances in order to confirm or refute clinical allergy. Further details regarding an oral food challenge may be found in a separate entry (chapter by Edwin Kim).

Non-IgE-mediated Food Allergy

Non-IgE-mediated, or cellular, allergic reactions to food include diseases such as dermatitis herpetiformis, food-induced pulmonary hemosiderosis (Heiner's syndrome), celiac disease, food protein-induced proctocolitis, and food protein-induced enterocolitis syndrome (FPIES).

Food-induced pulmonary hemosiderosis (Heiner's syndrome) is a rare syndrome seen in infants presenting with recurrent pneumonia with

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pulmonary infiltrates, hemosiderosis, gastrointestinal blood loss, iron-deficiency anemia, and failure to thrive (Metcalfe et al. 2008). Cow's milk precipitins may be detected and symptoms resolve with removal of cow's milk from the diet.

IgG, IgA, and IgM have been found to have a role in the disease pathogenesis of celiac disease (CD), and IgA antibodies play a role in its cutaneous manifestation, dermatitis herpetiformis (DH) (Metcalfe et al. 2008). CD is diagnosed based on serology detecting IgA to endomysium and tissue transglutaminase while the patient is ingesting a gluten-rich diet. A small bowel biopsy will confirm diagnosis and typically reveals atrophic mucosa with loss of folds, visible fissures, and a nodular appearance. Classic symptoms of CD include diarrhea, steatorrhea, weight loss or failure to thrive, and bloating. Atypical symptoms of CD are myriad and may delay diagnosis (Metcalfe et al. 2008). DH presents with chronic, intensely pruritic, polymorphic, vesicular, and bullous lesions at extensor surfaces of the elbows, knees, buttocks, and scalp and is characterized by the deposition of IgA granules at the dermoepidermal junction. The long-term treatment for CD and DH is a gluten-free diet.

FPIES reactions, in contrast to IgE-mediated reactions to foods, typically present with repetitive emesis 2 h or more after ingestion of the insulting food and may be accompanied by severe diarrhea as many as 6 h after ingestion. Cow's milk and soy are the most common foods causing FPIES. Rice, grains, meats, and fish have also been implicated (Metcalfe et al. 2008). Diagnosis is reliant on history and confirmatory food challenges in a controlled setting may be necessary. Food protein-induced proctocolitis and FPIES are discussed in detail in a separate entry (chapter by Michele Henson).

Mixed IgE/Non-IgE-Mediated Food Allergy

Examples of mixed IgE/non-IgE-mediated food allergy include eosinophilic esophagitis (EoE), eosinophilic gastroenteritis (EG), and atopic dermatitis. Literature regarding the recognition, diagnosis, pathogenesis, and treatment of EoE has increased numerous fold over the past decade. Symptoms vary with age, presenting as failure to thrive, frequent emesis, and abdominal pain in young children and with dysphagia and food lodging in adolescents and adults. Treatment options include dietary interventions (e.g., specific food elimination diets, avoidance of common food allergens, and elemental diets) or topical steroid (e.g., swallowed budesonide or fluticasone) (chapter by Brian Vickery).

Atopic dermatitis (AD) is characterized by extreme pruritus and a chronic relapsing course. Typical presentation begins in infancy and may persist into adolescence and adulthood. Triggers identified in patients with AD include aeroallergens, food allergens, bacteria (e.g., *Staphylococcus aureus*), and fungi (e.g., *Malassezia furfur*) (Metcalfe et al. 2008). Food allergens are more commonly identified in children with moderate to severe AD with studies showing approximately 35 % of children in this group having IgE-mediated food allergy to the most common food allergens, peanut, egg, milk, wheat, and soy (Eigenmann et al. 1998). Treatment recommendations for children with AD start with a consistent, intense skin moisturization plan in conjunction with treatment of any skin infections in addition to avoidance of irritants and known triggers. A systematic review of randomized controlled trials of food avoidance in patients with AD reports that there is no benefit of food avoidance in unselected patients with AD, but there may be benefit in avoidance of food triggers identified and confirmed by testing in select patients with AD (Bath-Hextall et al. 2009). Overly restrictive food avoidance may lead to nutritional deficiencies and not lead to improvement in AD; therefore, it is imperative to accurately confirm food triggers based on testing and observed food challenges when necessary.

Current Treatments and Future Therapies

The current standard of care for the treatment of food allergy is avoidance of the allergenic food

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and treatment of accidental ingestion with epinephrine (Boyce et al. 2010). Most children develop tolerance over time to food allergens such as milk, eggs, wheat, and soy, but allergies to foods such as peanuts, tree nuts, fish, and shellfish may be lifelong for the majority of affected individuals. Studies have shown that children avoiding milk or two or more food allergens are at risk for growth deficiencies compared to their nonfood allergic peers (Christie et al. 2002). Attention should be given to the complete diet of children with food allergies in order to ensure appropriate avoidance and adequate nutritional supplementation (chapter by Lesley Stanford).

Investigators have explored the utility of giving progressively larger amounts of the allergenic food over time with a process referred to as specific oral tolerance induction (SOTI) or oral immunotherapy (OIT). Other modalities under investigation include giving small amounts of the allergenic protein under the tongue, known as sublingual immunotherapy (SLIT), epicutaneous application of allergen via a process known as EPIT (epicutaneous immunotherapy), administration of Chinese herbal therapies, use of monoclonal antibodies against IgE, and the utility of ingestion of a noninfectious porcine parasite known as *Trichuris suis ova* (TSO) (chapters by Pooja Varshney and Stacie Jones and Robert Pesek).

Conclusions

Food allergy results from an interaction between the immune system and food and may lead to symptoms ranging from failure to thrive and food impaction (EoE) to life-threatening anaphylaxis. Diagnosis begins with a thorough history and application of specific, targeted tests. Education regarding food avoidance plays a vital role for safety, and nutritional supplementation is often necessary to ensure there are no avoidances which might lead to growth and developmental deficiencies. Investigational therapies are likely to improve the quality of life for affected individuals and their families in the future.

Cross-References

- ▶ Allergic Proctocolitis and Food Protein-Induced Enterocolitis Syndrome (FPIES)
- ▶ Cow's Milk Allergy
- ▶ Delayed Anaphylaxis to Mammalian Meat (Alpha-Gal)
- ▶ Diagnostic Food Challenges
- ▶ Eosinophilic Esophagitis
- ▶ Eosinophilic Gastrointestinal Disorders
- ▶ Epidemiology of Food Allergy
- ▶ Food Allergies, Diagnostic Testing
- ▶ Food Allergy and its Future Treatment
- ▶ Food Desensitization
- ▶ Nutrition in Food Allergy
- ▶ Peanut Allergy

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Food Desensitization

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Synonyms

Food immunotherapy; Oral desensitization

Definition

Allergen desensitization refers to a temporary state of reduced sensitivity to an allergen that is dependent on regular exposure to the agent. Food desensitization is the process by which a food-allergic individual is given increasing doses of a food allergen in order to diminish the allergic response to that food protein.

Background

Food allergy is a major health concern for which no active treatment is available. Current management strategies focus on strict allergen avoidance, early recognition of symptoms, and ready access to self-injectable epinephrine. Despite strict avoidance, affected individuals frequently encounter hidden allergens, and accidental reactions are common and can be severe. Fear of this outcome produces anxiety, disrupts social and educational activities, and profoundly impairs quality of life.

Current research efforts are exploring various active treatment options for food allergy. Food desensitization is one avenue being investigated as a potential therapeutic modality, and several recent studies have demonstrated evidence of reduced allergic responses as well as laboratory changes suggesting immune modulation.

Current Research

Food immunotherapy aims to change the immune response to food allergens. One goal of immunotherapy is desensitization, raising the threshold of food needed to cause an allergic reaction to a level that would provide protection against typical accidental exposures.

Subcutaneous peanut immunotherapy has been studied but was associated with a high rate of systemic reactions (Nelson et al. 1997). Several alternatives, including sublingual immunotherapy (SLIT), oral immunotherapy (OIT), and immunotherapy using extensively heated food allergens, are currently being investigated. In sublingual immunotherapy, the food protein is administered in solution form as drops held under the tongue for a period of time and then either spit out or swallowed. In a study of hazelnut sublingual immunotherapy, the mean quantity of hazelnut triggering allergic symptoms significantly increased in the active treatment group, while those receiving placebo had no significant change in allergen threshold (Enrique et al. 2005). Subjects receiving hazelnut SLIT also had significant increases in IgG4 and IL-10 levels, changes not seen in those receiving placebo. Of note, over half of the subjects had oral allergy symptoms at entry challenge.

Sublingual immunotherapy is showing promise in the treatment of food allergies associated with systemic symptoms, such as peanut (Kim et al. 2011) and milk (Keet et al. 2012). After 12 months on therapy, subjects receiving peanut SLIT ingested 20 times more peanut protein than the placebo group (Kim et al. 2011).

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Treatment was safe, with primarily mild oropharyngeal side effects reported. Mechanistic studies demonstrated diminished allergic responses, with decreased skin prick wheal size and basophil responsiveness. Peanut-specific IgE levels initially increased and then decreased; peanut-specific IgG4 levels increased steadily over the study period. Milk SLIT was shown to have fewer systemic side effects when compared with oral immunotherapy but was less effective in inducing desensitization (Keet et al. 2012).

In oral immunotherapy, the food protein is swallowed, either in its native form (i.e., milk, whole peanuts) or as a powder mixed in a vehicle food (i.e., powdered milk, peanut flour). Several trials of oral immunotherapy for food allergy have been undertaken, including studies in milk-, egg-, and peanut-allergic subjects. Treatment with milk or egg OIT has been successful in inducing desensitization, although a subset of subjects are recalcitrant to therapy, and further study is required to identify the profiles of optimal OIT candidates (Patriarca et al. 2003; Meglio et al. 2004; Staden et al. 2007; Buchanan et al. 2007; Longo et al. 2008; Skripak 2008; Keet et al. 2012). OIT for peanut allergy, which is generally lifelong, has also shown promise in early studies (Jones et al. 2009; Varshney et al. 2011). Clinical desensitization is a realistic goal and has been accompanied by laboratory changes indicating immune modulation, including decreased reactivity of mast cells and basophils, increased peanut-specific IgG4 antibodies, and eventually decreased peanut-specific IgE antibodies. Although peanut OIT is generally safe (Hoffmann et al. 2009; Varshney et al. 2011), a subset of patients do not tolerate treatment and reactions to previously tolerated doses do occur (Varshney et al. 2009). Additional study is required (see below; Thyagarajan et al. 2010); immunotherapy for food allergy remains investigational and should only be performed in research centers in the hands of experienced personnel.

Another form of "immunotherapy" being studied involves the use of extensively-heated or baked forms of egg and milk to potentially aid the induction of tolerance. Studies have shown that the majority of children with milk or egg allergy can tolerate baked forms of these foods (Nowak-Wegrzyn et al. 2008; Lemon-Mule et al. 2008). However, oral food challenge is the only method for identifying this subgroup of individuals, as no currently available laboratory markers reliably identify those who may tolerated baked milk or egg. Research is underway to study the safety and efficacy of introducing baked egg or milk into the diets of this subgroup as a form of immunotherapy.

Future Directions

Food allergen desensitization has shown promise as a potential treatment for food allergy. However, there remain numerous unanswered questions surrounding this investigational treatment, including the rate of side effects when compared to rate of accidental ingestion, optimal dosing regimen, patient selection, post-desensitization guidance, allocation of clinical resources, and reimbursement (Thyagarajan et al. 2010).

Thus far, most studies of food allergen immunotherapy have assessed *desensitization*, which refers to a temporary state of reduced sensitivity to an allergen that is contingent on regular exposure to the agent. In contrast, *tolerance* is defined as resolution of allergy without ongoing treatment – in other words, a long-term change in the immune response to a protein that persists once immunotherapy is stopped. Preliminary reports suggest tolerance is achievable in a subset of subjects receiving long-term food immunotherapy; further study is needed.

Cross-References

- ▶ Cow's Milk Allergy
- ▶ Egg Allergy
- ▶ Fatal Allergic Reactions to Foods
- ▶ Food Allergy and its Future Treatment
- ▶ Food Allergy, Overview
- ▶ Peanut Allergy

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Fragrance Contact Allergy

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Synonyms

Fragrance allergic contact dermatitis

Definition

Fragrance contact allergy is an adverse cutaneous reaction after exposition to a fragrance in an individual previously sensitized to that fragrance.

Introduction

Fragrances are ubiquitous in our society to which we are exposed in a continuous and daily basis. The best-known use is in commercial cologne perfumes. Furthermore, due to their odor properties and odor masking ability, they are widely distributed in cosmetics, household cleaning, industrial, topical medications, aromatherapy products, and even some foods or spices. This makes avoiding contact with these allergens

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a difficult, if not impossible, task for patients sensitized to fragrances.

Epidemiology

Fragrances are a large and heterogeneous group of chemical compounds and the second most common cause of contact allergy after metals. There are over 3,000 chemicals used as fragrances. Fragrances are a widely distributed allergen with which virtually all general population is in contact. However, the number of patients allergic to them is relatively small (Arribas 2012). The exact frequency of people allergic to fragrances in the general population is really hard to get. Estimated prevalence in the general population is 1.7–4.1 % according to findings from various studies (Cuesta et al. 2010).

Determining the prevalence of sensitization in patients with eczema who consult a dermatologist is somewhat easier, as confirmed in numerous articles on the subject. However, these data are thought to be underestimated, since patients often identify the problematic products and simply stop using them without consulting their physician. The percentages reported by the German Information Network of Departments of Dermatology (IVDK), which studied 40,790 patients from several European centers between 2005 and 2008 (Uter et al. 2010), were somewhat higher: 15.1 % of patients were sensitized to fragrances. According to the findings of the North American Contact Dermatitis Group, this prevalence increased to 23.4 % in the United States, with positive results to fragrance mix I in 11.5 % of cases and to balsam of Peru in 11.9 % (Rietschel and Fowler 2008). Some authors believe that these geographical variations could be partly due to the allergens used in testing, the differences in concentrations used, and the country-specific preferences for different fragrances.

Legislation and Safety

Two main organizations are responsible for regulating the use of fragrances in industry. The Research Institute for Fragrance Materials (RIFM) was founded in 1966 in the United States to generate, evaluate, and disseminate scientific data on the use of fragrances in consumer products. The IFRA (International Fragrance Association) was created in 1973 and is responsible for using these data to monitor safety in the use of fragrances and for creating industry codes of practice and guidelines. This organization makes recommendations on limiting or prohibiting the use of specific substances and on testing new fragrances to rule out toxicity before they come onto the market.

Despite the work carried out by these institutions, the ingredients used in industry have been kept secret for many years. In 2003, in accordance with the seventh amendment to the European Directive on Cosmetic Products, the European Union created a list of 26 ingredients that must be listed on cosmetic product labels if the content exceeds $\geq$10 ppm for leave-on products and $\geq$100 for rinse-off products. This list includes all the substances present in the fragrance mixes I and II used in patch tests. Some months later, the same measure was applied to household products, such as detergents and similar products. The directive, while adequate, could be improved, since several studies in Europe have revealed the need to review and modify the list of 26 allergens as a result of the discovery of new fragrances that cause contact eczema.

Clinical Features

Allergic contact dermatitis is the most common cutaneous adverse effect associated with the use of fragrances. It manifests mainly as subacute or chronic eczema caused by contact with fragrance allergens, a group of substances that are difficult to avoid in daily life. The typical patient is a 40-year-old woman with dermatitis affecting the hands or face, although any part of the body can be affected, depending on the type of product used and the area it is applied to (Johansen 2003). Most studies find the hands to be the site most commonly affected by cosmetic products and

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even more so by products used in the household and the workplace (Schnuch et al. 2004) (Heydom 2003).

Fragrances are seldom the only cause of hand eczema, and their application often complicates underlying conditions, such as irritant dermatitis and atopic dermatitis (De Grott and Frosch 1997). Some series find the face to be the most commonly affected site by direct application of cosmetic products, although airborne fragrances can also be responsible. Another frequently affected site is the legs in patients with vascular ulcers who become sensitized to the fragrance ingredients in their topical medication. A history of axillary eczema associated with deodorant or of cutaneous rash at sites where cologne or perfume is applied significantly increases the likelihood of a patient being allergic to fragrances. Fragrances are considered to be the most common cause of primary sensitization in this area. The neck is commonly affected by contact dermatitis due to fragrance allergy as a result of the direct application of perfumes and colognes. Cheilitis, which is usually a chronic disease, can be allergic in origin and caused by fragrances. A retrospective study of 129 patients with cheilitis found the second most common cause to be allergens found in cosmetic, dental, and food products (Schena et al. 2008).

Diagnosis

The information supplied by the patient leads to suspect fragrance allergy, especially when the area affected is one where a cosmetic product with a high fragrance concentration (e.g., cologne, perfume, or deodorant) is commonly applied. The history should include the cosmetic products used by the patient and exacerbating factors such as profession, hobbies, and exposure to sunlight.

In the physical examination, the presence of dermatitis on the face, retroauricular area, axilla, chest, or anal/vulvar area should alert the physician to the possibility of fragrance allergy. However, any part of the body can be affected.

Furthermore, other forms of dermatitis (irritant, atopic) can be complicated by sensitization to fragrances.

A confirmed diagnosis of allergic contact eczema is based on symptoms and patch testing, the results of which should be clinically relevant.

Allergens Used in Patch Tests

Of the more than 2,800 substances catalogued as fragrances by the RIFM, at least 100 are allergenic. Fortunately, the fact that only a limited number are responsible for most cases of sensitization facilitates detection of allergy using patch tests in which small groups of fragrances are analyzed together in mixes.

1. *Myroxylon pereirae* (Peru Balsam)

   It is the most widely used marker for diagnosis of fragrance allergy. This natural resin extracted from *Myroxylon pereirae*, a tree that grows in Central and South America, was originally used to heal wounds and cure infections. In 1974, the use of natural balsam of Peru as a fragrance ingredient was prohibited, and the use of its extracts and distillates in commercial products was restricted to a maximum concentration of 0.4 %. Today, we find it in perfumes, cleaning products, topical medications, dental cement and liquids, cosmetic products, and food aroma compounds.

   Balsam of Peru is composed of 250 chemical substances; the structure of at least 189 is known. Some of these components are fragrance allergens (e.g., cinnamyl alcohol, cinnamic aldehyde, eugenol, and isoeugenol).

   In 1948, Bonnevie reported that balsam of Peru was a common allergen and identified cinnamic aldehyde as an important allergic ingredient. Hausen tested the components of balsam of Peru in 102 patients who had a positive reaction to this marker and found the main culprit allergen to be a fragrance, cinnamyl alcohol (Hausen 2001). The second fragrance identified, eugenol, was the sixth most common allergen. The role of balsam of Peru as a marker of allergy to fragrances is more complex and heterogeneous than that of fragrance mix I. Balsam of Peru obtains

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a positive result in approximately 50 % of cases of fragrance allergy and has been reported to cross-react with colophony, balsam of Tolu, cinnamates, benzoates, benzyl salicylates, coumarin, farnesol, propolis, and diethylbestrol.

2. *Fragrance Mix I*
   Fragrance mix I, the first mixture used to test for fragrance allergies, was introduced as a marker in the standard series after the publications by Larsen in the late 1970s. It has eight components (seven synthetic fragrances and one natural fragrance: geraniol, cinnamaldehyde, hydroxycitronellal, cinnamyl alcohol, α-amylcinnamaldehyde, isoeugenol, eugenol, and Oakmoss). Initially, each of the fragrances was tested at 2 % (total of 16 %); however, this approach generated a large number of false-positive results because of irritant action. Therefore, in 1984, the concentration was reduced to 1 % (total of 8 %).

   In some of the series marketed, sorbitan sesquioleate 5 % is used as an emulsifier in both balsam of Peru and fragrance mix I. Enders et al. demonstrated that sorbitan sesquioleate improved the diagnostic value of these markers because it acts as a vehicle for the fragrances. The only disadvantage of this emulsifier is its occasional allergenic capacity. Consequently, some authors recommend including sorbitan sesquioleate in the specific fragrance series to rule it out as an allergen. In patients who have a positive reaction to both balsam of Peru and fragrance mix I, up to 17.7 % of reactions are false-positive and the patients are in fact allergic to the emulsifier (Johansen 2002).

   Balsam of Peru and fragrance mix I continue to be efficacious and detect between 70 % and 90 % of fragrance-allergic patients. Some authors have even identified fragrance allergy in up to 85 % of patients using only fragrance mix I. Nevertheless, in the last few years, new fragrance markers have been developed that reflect advances in the industry, which brings products with new fragrances onto the market. Recent findings show that around 15 % of fragrance-allergic patients are not detected by these two markers. Since 2005, experts have been studying the use of fragrance mix II and hydroxyisohexyl 3-cyclohexene carboxaldehyde (Lyral) as markers of sensitization to fragrance in some standard series in Europe.

3. *Fragrance Mix II*
   In 2005, Frosch et al. studied a new tool – fragrance mix II – with the aim of detecting a greater number of patients sensitized to fragrances, including those not diagnosed after the application of the usual markers. Fragrance mix II is composed of 6 fragrances at different concentrations (Frosch et al. 2005). In 2010, data collected by the IVDK were published on patients tested with this mix in several European centers between 2005 and 2008. Of the 35,633 patients included, 4.9 % had positive results with fragrance mix II; the most common allergens detected with this series, in decreasing order of frequency, were as follows: Lyral (in almost half of the sample), citral, farnesol, hexylcinnamal, coumarin, and citronellol (Krautheim et al. 2010).

   Most studies analyzing the usefulness of this mix agree with the recommendation that it should be included in the standard series, since it detects a considerable number of fragrance-allergic patients who would not be diagnosed by fragrance mix I and balsam of Peru (Heisterberg 2010). Negative reactions to fragrance mix I have been recorded in 32 % of patients with a positive reaction to fragrance mix II.

4. *Hydroxyisohexyl 3-Cyclohexene Carboxaldehyde*
   Hydroxyisohexyl 3-cyclohexene carboxaldehyde (Lyral) is included in fragrance mix II at a concentration of 2.5 %; however, most authors recommend its inclusion in the standard series at double this concentration (5 %). The frequency of sensitization is 1–3.1 %, and it is often detected in patients with hand eczema.

Specific Fragrance Series

When one or two fragrance markers in the standard series (fragrance mix I, balsam of Peru, or

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both) are positive, the specific fragrance series should be applied, although the yield is poorer when a positive result is obtained only for balsam of Peru, since in 75 % of these cases, we will not obtain a positive result for a specific fragrance.

The number of individual fragrance ingredients tested and the proportions used varies depending on the country and laboratory. The specific series should include all the fragrances in fragrance mixes I and II individually. It should also include the 26 fragrances that must be specified on product labels, since a positive result for any of these substances would allow us to advise the patient to avoid only the specific fragrances.

Sorbitan sesquioleate should be tested individually as part of this specific series, since it enables to detect false-positives in patients with a positive reaction to either of the mixes caused by allergy to the emulsifier rather than to the fragrance. Other authors recommend including this emulsifier in each of the fragrances to increase the diagnostic yield of the series and avoid false-negatives.

Products Used by the Patient

The allergy workup can be completed by testing the products used by the patients, especially if those products are suspected of causing dermatitis. Depending on the product, it can be applied as a patch test or a repeat open application test. The latter method is recommended in the case of highly irritant products, such as colognes or perfumes. In the case of products whose daily application involves removal or rinsing from the skin (e.g., shampoos and shower gels), the undiluted product should not be used in patch tests or use tests. The concentration should be reduced to 1 % aq. or the repeat open application test method should be used, since these approaches can confirm the clinical relevance of the results in some cases.

Patch Test Readings

European baseline series includes the four fragrance allergy markers previously mentioned. If a positive reaction is observed in one or more of these, the specific fragrance series should be tested. According to De Groot and Frosch, if the reaction is weakly positive, the probability of it being an irritant is high; therefore, the authors recommend reapplying the marker in a patch test before applying the specific series.

Studies show that no positive reactions are detected with the specific series in 25–60 % of patients who react to fragrance mix I. There are several possible explanations for this finding. First, the positive response to the mix could be irritant, that is, a false-positive. Second, the result may be a false-negative to the specific series, because the concentration of the individual fragrances is too low or because the fragrances do not contain the emulsifier sorbitan sesquioleate, which enhances the absorption of these substances and is included in the mixes of the standard series. Third, the patient could react to a combination of several fragrances and not only to an individual fragrance. A synergistic effect may occur when several fragrances are combined.

If positive results are obtained for both fragrance mix 1 and balsam of Peru in the standard series, it is more likely that the allergy is actually to fragrances. Nevertheless, it is important to rule out sensitization to sorbitan sesquioleate, the emulsifier that is added to these markers in some series. This can be done by testing it separately in the specific fragrance series.

Only 25 % of patients who have a positive result for balsam of Peru will show a positive result when tested with the specific series. Despite the poorer yield, we feel that this approach is worthwhile, since one-quarter of these patients will only have to avoid one fragrance rather than stop using all of them (Cuesta et al. 2010).

If both fragrance mixes I and II are positive at hospitals that use them as part of their standard series, we should consider cosensitization to geraniol and citral, which could be confirmed by applying the specific series.

In the hypothetical case where the clinical suspicion of contact allergy to fragrances is high despite negative patch test results, it is adequate to test the specific fragrance series because in more than 9 % of cases, a positive result to at least one fragrance and, therefore, a diagnosis will be obtained (Arribas et al. 2013).

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Management

The treatment of fragrance-allergic patients has proven problematic because of the ubiquitous nature of these substances and, until recently, the secrecy surrounding the ingredients of marketed products. Therefore, a diagnosis of fragrance allergy used to involve restricting any product containing fragrances.

Since the implementation of the European law regulating mandatory specification of some of the more common fragrances in household and domestic products, treatment has changed radically, although certain limitations remain.

Several scenarios can be envisaged, depending on the results of patch tests. If a positive result for one of the fragrance markers is followed by one or more positive results in the specific fragrance series, it is recommended to advise the patient to avoid only those ingredients and use products containing other fragrances.

In 75 % of cases with a positive result for balsam of Peru and in 10–40 % of patients who had positive results for fragrance mix I, a definite culprit allergen after testing with the specific fragrance series is not found. In this case, if the markers yield positive results after repeat testing, patients with reactions to balsam of Peru should use only fragrance-free cosmetic, household, and occupational products. Patients allergic to balsam of Peru who experience severe and extensive skin disease could benefit from a diet free of spices such as cinnamon and clove, as well as curry mixes.

Primary preventive measures that can be applied before contact sensitization occurs include regulation of the maximum permissible concentration of fragrances in commercial products and the creation of new synthetic substances with less allergenic potential than the original products.

Conclusions

Contact dermatitis due to fragrance allergy is common. The markers included in most standard series for detection of fragrance allergy (fragrance mix I and balsam of Peru) are good, but there is room for improvement. In recent years, new markers (fragrance mix II and Lyral) have been developed and included in the series of other countries. These markers have proven useful for detecting fragrance-allergic patients who previously went undiagnosed.

The specific fragrance series should be applied when the patient tests positive to a fragrance marker, since in most cases specific testing will identify one or more fragrances that are, at least in part, responsible for the patient's skin disease.

Identifying the specific fragrance allergen has become even more important since the implementation of the law requiring 26 fragrance ingredients to be specified on the labels of commercial products. Before this legislation was enacted, patients diagnosed with fragrance-induced allergic dermatitis faced considerable restrictions on their lifestyle, and the allergy represented a therapeutic challenge for the dermatologist.

Cross-References

- ▶ Allergic Contact Dermatitis
- ▶ Fragrancy, Allergic Contact Dermatitis

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Fragrancy, Allergic Contact Dermatitis

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Definition

There are more than 5,000 different fragrances known today. Each product may contain more than one fragrance, but only a small number of fragrances are identified as common sensitizers and causers of allergic contact dermatitis. A fragrance mix consisting of eight individual fragrances has been developed to screen for fragrance allergy. This screen consists of cinnamic alcohol, cinnamic aldehyde, eugenol, isoeugenol, geraniol, alpha amyl cinnamic alcohol, hydroxycitronellal, and oak moss absolute. The fragrance mix is used as a patch test and detects approximately 75 % of fragrance allergic cases. An estimated 1–2 % of the general population is allergic of fragrances. Fragrances do not only occur in cosmetics and perfumes, but they can also be found in the workplaces, in paints, cutting fluids, and metal working fluids, where they mask offending odors. Fragrances may also circulate through air-conditioning.

The therapy consists basically of symptomatic treatment of the clients and avoidance of the allergens.

Cross-References

▶ Allergic Contact Dermatitis
▶ Contact Urticaria and Protein Contact Dermatitis (to Asparagus, Cow's Hair, Seafood, Etc.)
▶ Dermatitis from 2-*N*-Octyl-4-Isothiazolin-3-One, Allergic Contact
▶ 3-Dimethylaminopropylamine (DMAPA), Allergic Contact Dermatitis to
▶ Emergent Allergies in Cosmetics
▶ Eyes and Eyelid, Contact Allergic Reaction On
▶ Herbal Remedies
▶ Methods (In Vivo): Skin Test (Intradermal, Puncture)
▶ Occupational Contact Dermatitis Due to Acrylates and Methacrylates
▶ Photoallergic Contact Dermatitis

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Genetic Regulation of IgE

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Definition

Genetic regulation of IgE: influence of genes and variations of genes (polymorphisms) on the propensity of producing immunoglobulin E (IgE) in humans.

Introduction

Atopic diseases such as atopic dermatitis, allergic asthma, allergic rhinitis, and food allergy are based on genetic determinants with a reported heritability of up to 80 % (Cookson and Moffatt 2000; Vercelli 2008; Gould and Sutton 2008). Atopic diseases are typical complex, polygenic traits, which are believed to be influenced by the environment, gene–gene interactions, and multiple genetic variants. A large number of candidate gene studies have been conducted for atopic diseases, results of which were often inconsistent. The candidate genes that could be determined confer either a disease-specific risk or appear to be important for the atopic state rather than for a specific atopic disease. The exclusive assignment of association to either a disease-specific risk or the atopic state very much confines the observations of clinicians in the field. Allergologists frequently observe a state of total and specific IgE-antibody elevation without any sign of clinical symptoms suggestive of an atopic disease (Illi et al. 2004). The regulation of serum IgE production is largely influenced by familial determinants. Twin-based and pedigree-based studies revealed evidence for a strong genetic contribution to the variability of total IgE levels (Strachan et al. 2001). Family and case control studies in addition have indicated that total serum IgE levels are largely determined by genetic factors that are independent of specific IgE levels. The genetic control of total IgE is even stronger than atopic disease (Strachan et al. 2001).

Genetic Regulation of Total IgE

Mostly candidate gene studies investigated total IgE as secondary trait. The genome-wide association study by Weidinger et al. (2008) used total IgE as the primary outcome variable. Significant associations were found between total IgE and the promoter region of the gene encoding the alpha chain of the high affinity receptor for IgE (***FcER1A***; *rs2251746 and rs2427837*), multiple single nuclear polymorphisms (SNPs) within the ***RAD50*** gene, and the ***STAT6*** gene. Confirmation

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to the *FcER1A* rs2251746 relevance was given by a birth cohort study with a follow-up until the age of 6 years. This particular study did not find an association between the clinical traits asthma, rhinitis, and eczema (Chen et al. 2009). *RAD50* encodes a DNA repair enzyme, but it clusters into the Th2 cytokine cluster, which is characterized by tight linkage equilibrium across the region. Moreover, it contains several candidate genes for atopy-related traits (IL13; rs1800925, rs20541) (Ober and Hoffjan 2006). More recently, a ***SOCS-1*** promoter variant (*SOCS1*+ 1125 G > C; rs33932899) has been found to have significantly lower levels of serum IgE compared to those that are homozygous for the G-allele (Mostecki et al. 2011). In addition, it could be shown that the *SOCS1*+ 1125 G > C SNP was in complete linkage disequilibrium with a SNP at position *SOCS1*-820 G > T (rs33977706) of the *SOCS1* promoter. Carriers of the T-allele at the *SOCS1*-820 G > T were also found to be associated with decreased IgE (Mostecki et al. 2011).

Limitations of Factors Regulating IgE Responses

The search for genetic variants that can modulate IgE responses is intense, and is based on both candidate gene approaches and linkage studies followed by positional cloning (Vercelli 2005; Weidinger et al. 2010; Vercelli 2010). Although loci and genes likely to be major determinants of susceptibility to allergic inflammation in human beings have been described (Hoffjan et al. 2003), two main difficulties typically arise: one across genes and chromosomes and the other along a gene and a chromosome. The hits generated by genetic studies almost invariably involve multiple loci and genes, but few if any of them give strong signals individually. This fact is not restricted to allergy and asthma (Sleiman et al. 2010; Mathias et al. 2010). Indeed, the distribution of individually small defects among pathways that cooperate to increase disease susceptibility (often, if not always, in combination with environmental influences) is the unifying feature of complex diseases. The "across genes and chromosomes" difficulty arises from linkage disequilibrium (LD). In the majority of cases, variants within a certain gene are in tight linkage disequilibrium (LD) which implies they occur together as a group, and LD blocks can extend for long genomic distances, occasionally reaching into neighboring genes. This makes the mechanistic interpretation of genetic data difficult, if not impossible (Fig. 1).

Genetic Determinants of Cord Blood IgE Regulation

Genetic determinants of cord blood IgE have recently been investigated to support the notion that the perinatal phase is a major influencing factor. Authors have tested the associations between functional or tagging single nucleotide polymorphisms (SNPs) in genes involved in the TH1/TH2 pathway and cord blood (CB) IgE in a large US inner-city birth cohort (Hong et al. 2010). More specifically, the study focused on genes in the TH1 pathway (e.g., IL-2, IL-12, IL-18, interferon g [IFNG]); TH2 pathway (e.g., IL-4, IL-13, IL-4 receptor [IL4R], IL-13 receptor alpha 1 [IL13RA1], IL-5, IL- 5 receptor alpha [IL5RA], Janus kinases [JAKs], signal transducer and activator of transcription 6 [STAT6]), and the Treg cell pathway (e.g., forkhead box P3 [FOXP3], IL-10, and transforming growth factor b1 [TGF-B1]). Besides this, ethnic heterogeneity and gene–gene interactions in relation to CB-IgE have been explored. Three SNPs (rs1800925, rs2069743, and rs1295686) in the IL-13 gene were significantly associated with CB-IgE concentration ($P < 6x10^{-4}$, FDR-corrected $P < 0.05$). These SNPs jointly influenced CB-IgE in a dose–response manner (P for trend $9x10^{-8}$). Significant associations also were observed for SNPs in the IL-13 receptor α1 (rs5956080) and STAT6 (rs11172106) genes. Ethnicity-specific genetic effects were observed for SNPs in the IL-5 and GATA3 genes. Several gene–gene interactions (including IL-13–IL-4 receptor and IL-13–signal transducer and activator of transcription 6 interactions) were detected in relation to CB-IgE. Ultimately, the data

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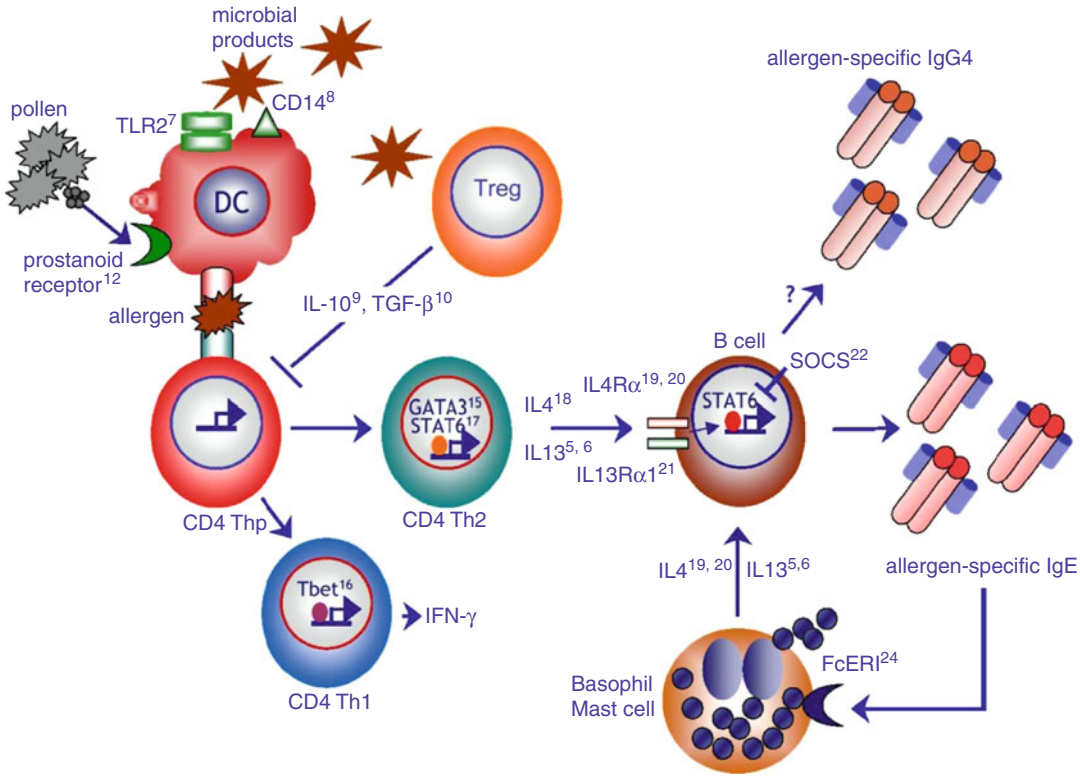

Genetic Regulation of IgE, Fig. 1 Gene–gene interactions and the pathogenesis of allergic inflammation Groups of interactions are color-coded: The regulatory and sensing interfaces are in red/orange, TH differentiation is in blue/green, and the effector phase is in shades of brown. For some of the genes encoding these molecules, association or linkage studies exist and are referenced. For others, associations were found with phenotypes other than IgE (e.g., asthma), but these genes are included because asthma and increased IgE levels frequently co-occur. For still others (labeled with a question mark), a role in these processes is proposed but not yet proven. References and figure is taken from Vercelli D (2005) (reference numbers in the figure relate to references of the original publication)

demonstrate that multiple SNPs are individually and jointly associated with CB-IgE, with evidence of gene–gene interactions and ethnic heterogeneity, suggesting that genetic regulation of IgE may begin in utero (Hong et al. 2010) (Fig. 2).

Cellular Mechanisms in IgE Regulation

Beyond the genetic regulation of total IgE, and more downstream, the control of IgE synthesis is regulated by a two-signal model. The molecular mechanisms of this process are covered and reviewed extensively elsewhere. In the model, interplay between T and B lymphocyte signal 1 covering the ε germline transcription involves the cytokines IL-4 and IL-13. Signal 2 mediating B-cell activation and switch recombination might be engaged by CD40 involvement, EBV infection, and corticosteroids. While other cytokines such as BAFF (B-cell activating factor belonging to the tumor necrosis factor family) and APRIL (a proliferation-inducing ligand) can induce both T cell-independent and T cell-dependent class switching to IgE (at least in vitro), it is thought that CD40–CD40L and AID (activation-induced deaminase) are required for significant in vivo IgE production. B-cell activation via Toll-like receptor 4 (TLR4) also

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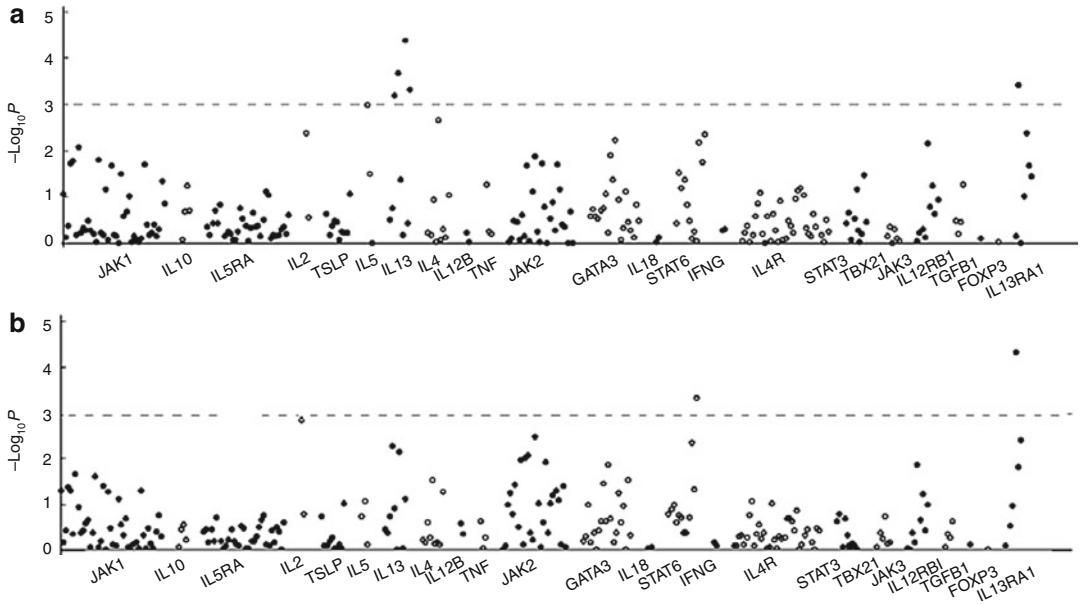

Genetic Regulation of IgE, Fig. 2 SNP associations with log10-transformed cord IgE concentration (**a**) and detectable cord IgE ((**b**); 249 SNPs on 23 genes) The associations are adjusted by maternal age, maternal BMI, maternal atopic history, previous deliveries, previous pregnancies, infant's sex, household income, season of birth, and individual ancestral proportion. GATA3, GATA-binding protein 3; IL, interleukin; IL12B, interleukin 12 b; IL12RB1, interleukin 12 receptor b1; JAK1, Janus kinase 1; JAK2, Janus kinase 2; JAK3, Janus kinase 3; STAT3, signal transducer and activator of transcription 3; TBX21, t-box 21; TNF, tumor necrosis factor; TSLP, thymic stromal lymphopoietin (Hong et al. 2010)

effectively induces IgE class switching. Other molecules displaying particular regulatory roles are IL-21, STAT3, IL-25, TSLP and are under investigations in vitro and/or in vivo studies (Mostecki et al. 2011).

New Developments

Genome-wide association studies (GWAS) have in common, that only a small fraction of disease heritability is covered by the associated genetic variants. This may be due to the fact that variants with small individual effects might have larger effects when considered in interaction with other unknown factors. GWAS currently missed this phenomenon. Another explanation provides the fact, that a large proportion of "missing heritability" is attributable to low-frequency variants with intermediate penetrance, which should be overcome by the next-generation GWAS products (Wang et al. 2010; Weidinger et al. 2010).

Cross-References

- ▶ Genetic Regulation of IgE
- ▶ IgE Isotype Switching
- ▶ IgE Receptor
- ▶ IgE Testing

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Gluten Intolerance and Skin Diseases

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Synonyms

Celiac disease; Dermatitis herpetiformis Duhring; Gluten sensitivity; Nontropical sprue

Definition of Gluten Intolerance

In general gluten sensitivity is mainly considered to be linked with celiac disease (CD).

Common denominator for all patients with celiac disease is the presence of a variable combination of the following:

- Gluten-dependent clinical manifestations
- Specific autoantibodies
- HLA DQ2 and/or DQ8 haplotypes
- Different degrees of enteropathy (Troncone and Jabri 2011)

However, reports of gluten sensitivity without celiac disease date to 1978, when a patient with normal small bowl biopsies and diarrhea was described which improved within days after starting a gluten-free diet (El-Chammas and Danner 2011). Marsh's "modern" definition of gluten sensitivity describes "a state of heightened immunological responsiveness to ingested gluten in genetically-predisposed individuals," with such responsiveness being expressed also in organs other than the gastrointestinal tract (El-Chammas and Danner 2011; Marsh 1995).

Regarding skin manifestations of gluten sensitivity, the most important and most closely linked disease surely is dermatitis herpetiformis (DH). Furthermore, there are a variety of symptoms and skin diseases which may as well be influenced by gluten sensitivity.

Dermatitis Herpetiformis

Definition

Dermatitis herpetiformis is by many considered as a cutaneous manifestation of celiac disease (Troncone and Jabri 2011).

Epidemiology

DH is a lifelong disease that can appear at any age. The common age at onset of DH is 30–40 years, but DH can also appear at older ages or even in childhood (Reunala 2001).

Men have a higher prevalence of DH than women with male to female ratios ranging from 1.5:1 to 2:1. The opposite is true for the prevalence of CD, with female to male

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ratios ranging from 2:1 to 4:1. DH is most often seen in patients of Northern European descent (Bolotin and Petronic-Rosic 2011a). These differences in geographical distribution of DH may be dependent both on immunogenetic (HLA) and environmental factors, such as high or low consumption of wheat and related cereal products (Reunala 2001).

Pathogenesis

The pathophysiology of DH involves a complex interaction between genetic, environmental, and autoimmune factors.

The inflammatory processes of DH and CD seem to be closely linked. Virtually all patients with DH have an associated enteropathy, although the severity of the skin disease does not correlate with the degree of the enteropathy (Zone 2005). If patients with DH adhere to a strict gluten-free diet for several months to years, cutaneous IgA and C3 deposits decrease and may disappear, while IgA immune complexes return when resuming gluten consumption. It is assumed that IgA-containing circulating immune complexes originate from the gut. These circulating immune complexes can be detected in sera of patients with DH, and increased levels have been found after wheat ingestion (Reunala 2001).

Gluten encompasses a group of storage proteins of wheat, barley, and rye. Even though gluten is the exogenous antigen for both celiac disease and DH, these two diseases have characteristics of autoimmune disorders (Marietta et al. 2008).

Important autoantigens seem to be transglutaminases. The family of transglutaminases consists of enzymes which are ubiquitous expressed. Three of nine isoenzymes have been identified as crucial autoantigens in CD and related diseases (Sardy and Tietze 2009). Tissue transglutaminase (tTG) is the major autoantigen targeted in CD and epidermal transglutaminase (eTG) is the autoantigen most closely linked to DH (Sardy et al. 2002; Bolotin and Petronic-Rosic 2011a).

In patients with CD, tTG is found in elevated concentrations in the gut. Here tTG deamidates the alcohol-soluble fraction of gluten known as gliadin, thus resulting in the formation of multiple negatively charged glutamin acids (Sardy and Tietze 2009). Modified gliadin is highly immunogenic when bound to HLA DQ2 or HLA DQ8 on antigen-presenting cells (Bolotin and Petronic-Rosic 2011a).

Additionally tTG may be cross-linked to gliadin forming complexes which also show immunoreactivity in the context of presentation by HLA DQ2 or HLA DQ8 molecules to T cells (Sardy and Tietze 2009; Bolotin and Petronic-Rosic 2011a). Activation of T cells leads to the production of tTG-specific autoantibodies and subsequently to an inflammatory tissue response (Schuppan et al. 2009).

The importance of a genetic predisposition has been shown in several epidemiologic studies. For example, it has been shown that more than 90 % of patients with CD express the MHC class II molecule HLA DQ2 and almost all others HLA DQ8 in comparison to approximately 30–40 % of control patients. Furthermore, in monozygotic twins with CD or DH, there is 70 % concordance (Troncone and Jabri 2011). The association between DQ2 and CD or DH is one of the strongest observed between the class II region genes and autoimmune diseases (Reunala 2001).

Epidermal transglutaminase (eTG) is produced both in the gut and the skin. IgA autoantibodies to eTG develop late in the evolution of CD. Thus, epitope spreading might be responsible for the development of IgA eTG antibodies in a subset of patient who then develop DH. These patients tend to be less severely affected by CD with prolonged gluten exposure finally promoting epitope spreading (Zone et al. 2011). In normal skin, expression of eTG is found in the upper epidermal layers, stratum corneum, and hair follicles. eTG is thought to be involved in the maturation of the cornified layer. It appears to be released either by externalization or after breakdown of the keratinocyte cell membrane during the formation of the cornified layer. Most likely, eTG then diffuses from the epidermis through the epidermal basal membrane and aggregates in the papillary dermis, where it is bound by IgA autoantibodies. No tissue-fixed eTG has been identified in the normal skin. Indirect immunofluorescence with DH serum usually shows negative results, since the antigen is normally not

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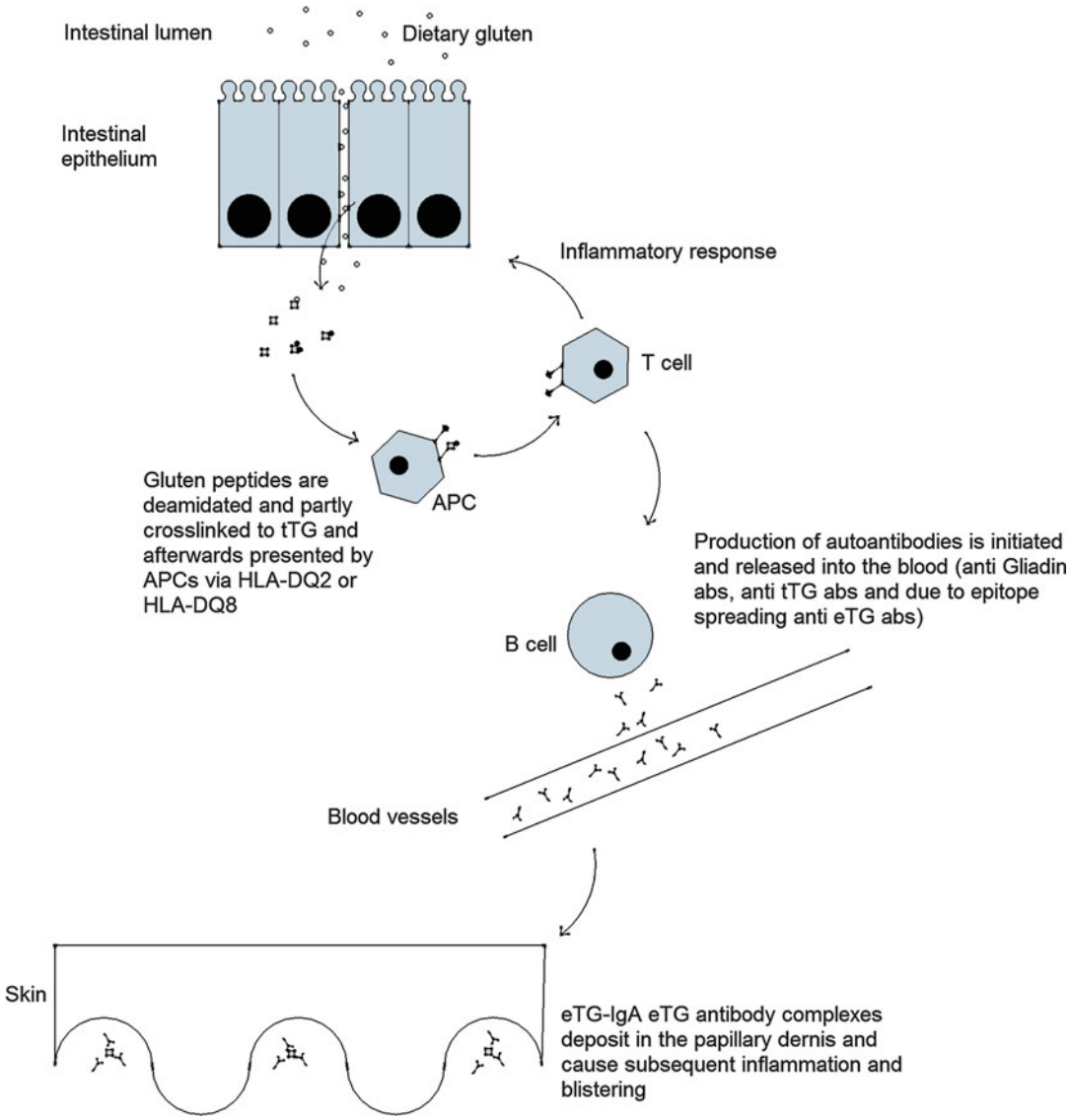
Intestinal lumen
Dietary gluten
Intestinal epithelium
Inflammatory response
T cell
APC
Gluten peptides are deamidated and partly crosslinked to tTG and afterwards presented by APCs via HLA-DQ2 or HLA-DQ8
Production of autoantibodies is initiated and released into the blood (anti Gliadin abs, anti tTG abs and due to epitope spreading anti eTG abs)
B cell
Blood vessels
Skin
eTG-IgA eTG antibody complexes deposit in the papillary dernis and cause subsequent inflammation and blistering

Gluten Intolerance and Skin Diseases, Fig. 1 Schematic of the hypothetical pathogenesis of dermatitis herpetiformis

present, except as a minor soluble component in this location (Zone et al. 2011). The dermal deposition of IgA is thought to trigger an inflammatory response (Bolotin and Petronic-Rosic 2011a). Neutrophilic microabscesses appear in the papillary dermis and are quickly transformed by edema into microvesicles which then coalescence to form subepidermal blisters. The split occurs in the lamina lucida (Reunala 2001; Bolotin and Petronic-Rosic 2011a). While the predominant autoantibodies are of the IgA class, likewise IgG can be found. IgG autoantibodies might be especially important in patients with gluten sensitivity and IgA deficiency (Bolotin and Petronic-Rosic 2011a) (Fig. 1).

Clinical Picture

The primary lesions of DH are small grouped papulovesicles, which are rapidly eroded by scratching due to the intense pruritus; thus,

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Gluten Intolerance and Skin Diseases, Fig. 2 Clinical picture shows grouped excoriated papulovesicles

often only excoriated papules are clinically observed (Zone 2005; Bolotin and Petronic-Rosic 2011a; Kneisel and Hertl 2011a). Therefore the location of the lesions is more important than the kind of efflorescence (Sardy and Tietze 2009). The classic distribution involves bilateral extensor surfaces, scalp, and buttocks. Mucosal involvement is rare. An uncommon skin manifestation of dermatitis herpetiformis is palmoplantar purpura. This finding is more common in children. Clinically petechiae are present on the palms and/or soles (Hofmann et al. 2009; Bolotin and Petronic-Rosic 2011a) (Fig. 2).

As DH is considered to be a cutaneous manifestation of CD, all patients with DH have some degree of CD (Zone 2005; Bolotin and Petronic-Rosic 2011a). Some patients only show jejunal histological findings but are asymptomatic for CD. But if there are gastrointestinal symptoms typical for CD as well as skin symptoms, the presumption diagnosis DH should be considered.

Diagnostics

The diagnosis of DH is dependent on the detection of granular IgA deposits in the dermal papillary tips of perilesional skin by direct immunofluorescence (Kneisel and Hertl 2011b). Of course, false-negative results may occur if a biopsy is performed directly from the visible skin lesions. This is believed to be secondary to the destruction of immunoreactants by the intense inflammatory process in the involved skin (Zone 2005; Bolotin and Petronic-Rosic 2011a). IgA deposits are found throughout the skin, but greater amounts seem to be present near active lesions (Reunala 2001) (Fig. 3).

Typical histopathologic features of DH are found in an early non-blistering lesion, and these consist of accumulation of neutrophils and a few eosinophils with formation of papillary microabscesses. This finding is, however, not specific because it occurs also in linear IgA disease (Reunala 2001).

Serologic testing is a useful adjunct to tissue-based studies. Circulating IgA antibodies to endomysium, the fine connective tissue sheath surrounding a muscle fiber, are detected both in CD and DH. Testing is based on indirect immunofluorescence using monkey esophagus as substrate and highly specific but only moderately sensitive for DH. IgA anti-tissue transglutaminase (tTG) and IgA anti-epidermal transglutaminase (eTG) tests are performed by enzyme-linked immunosorbent assay (ELISA) and show good specificity as well as sensitivity. The IgA anti-tTG testing is widely available, whereas the IgA anti-eTG has been relatively recently discovered and attracted increased interest since eTG is the key autoantigen of DH. Levels of anti-tTG and anti-eTG IgA correlate with the extent of small bowel pathology but are low or undetectable in patients following strict

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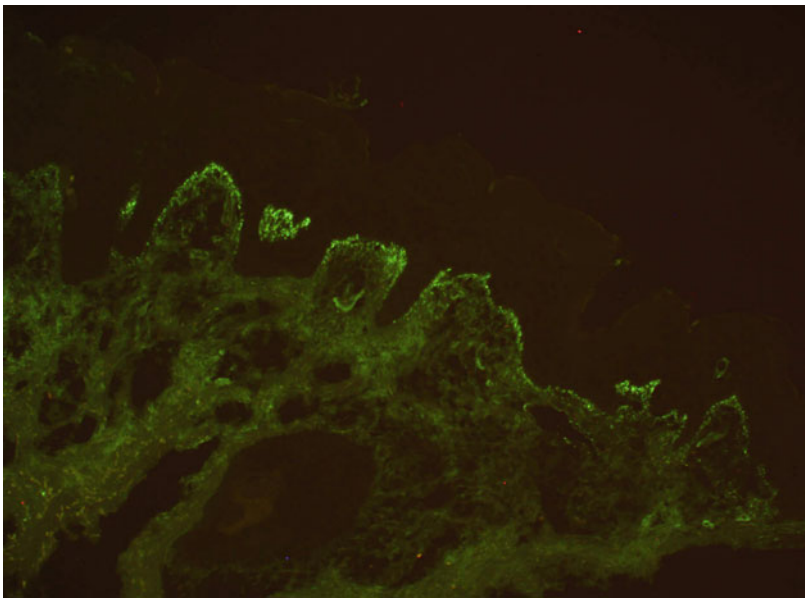
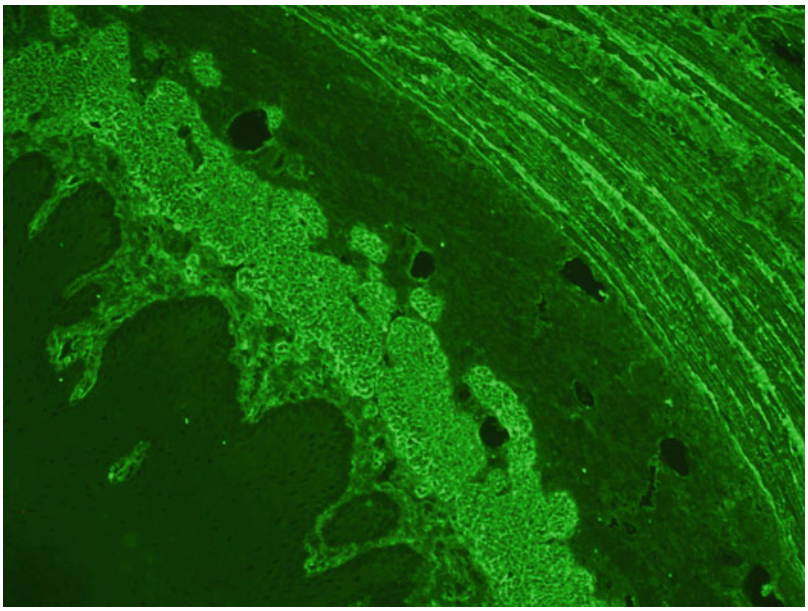


Gluten Intolerance and Skin Diseases, Fig. 3 Direct immunofluorescence shows granular-linear deposition of IgA along the dermo-epidermal junction zone



Gluten Intolerance and Skin Diseases, Fig. 4 Indirect immunofluorescence shows IgA staining of the endomysium enveloping the horizontally and vertically striped muscles

gluten-free diet and may therefore be used to monitor the adherence to the dietary regimen. Selective IgA deficiency may lead to a delay of diagnosis because of the lower detection rates of IgA autoantibodies through serologic testing (Rose et al. 2009; Bolotin and Petronic-Rosic 2011b) (Fig. 4).

In 75 % of the patients with DH, gastroscopic biopsies show classical jejunal villous atrophy since most of these patients have subclinical CD. Even the remainder still have minor mucosal changes with increased numbers of intraepithelial gamma/delta T lymphocytes (Reunala 2001).

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Therapy and Prognosis

DH is the only cutaneous autoimmune disease whose trigger (gluten) is known and which is completely curable through avoidance of gluten even without any immunosuppressive treatment. Therefore, a consequent diet is the therapy of choice (Sardy and Tietze 2009).

Approximately 2–4 years after the initiation of a gluten-free diet, the skin lesions will slowly dissolve. Meanwhile a symptomatic therapy with sulfonamides, mostly dapsone, can be applied. Dapsone suppresses the function and chemotaxis of neutrophils and therefore has an anti-inflammatory effect on the skin, but has no influence on the enteropathy (Zone 2005; Sardy and Tietze 2009). While the disease responds promptly to dapsone, glucocorticosteroids are not effective and thus an unsuccessful therapy with glucocorticosteroids has diagnostic value (Sardy and Tietze 2009).

Patients with DH as well as patients with CD have an increased risk for lymphoma. The risk of developing lymphoma may depend on long-lasting stimulation of lymphocytes, giving rise to malignant transformation. Gluten-free diet has shown to have a protective effect against the development of lymphoma in patients with DH (Reunala 2001).

Because of the influence of genetic predisposition in pathogenesis of DH, the screening of family members might be discussed (Bolotin and Petronic-Rosic 2011b).

Other Skin Manifestations of Gluten Sensitivity

Oral Ulcers

Oral ulcers can occur concurrently with CD and seldom also with DH. Five percent of patients with idiopathic oral ulcers having an associated CD were showing improvement under gluten-free diet (Jokinen et al. 1998). It has been demonstrated that 85 % of these patients had high levels of antigliadin antibodies (Troncone and Jabri 2011). Clinical appearance of concomitant dental abnormalities such as enamel defects is also observed frequently in these cases (Bolotin and Petronic-Rosic 2011a; Rashid et al. 2011).

Deficiencies

Deficiency of iron, vitamins of the B complex, folate, zinc, and other micronutrients can all occur in the absence of overt gastrointestinal symptoms in patients with CD. Iron deficiency is relatively common in CD and can be due to either malabsorption of iron or occult intestinal bleeding. Typical dermatological features of the above mentioned deficiencies are alopecia, pruritus, recurrent aphthous ulcers, angular stomatitis, or glossitis (Poon and Nixon 2001).

Association with Autoimmune Disorders

Some diseases, many with an autoimmune pathogenesis, are found with a higher than normal frequency in patients with CD (Troncone and Jabri 2011).

For example, there are findings of an increased incidence of CD in patients with alopecia areata. However, the observed hair regrowth after gluten-free diet has to be regarded with caution, since studies show a great variety and alopecia areata has a high rate of spontaneous remission (Poon and Nixon 2001; Zone 2005). Sporadic cases of vitiligo have been reported, but are probably coincidental (Humbert et al. 2006).

Urticaria, Psoriasis, and Others

Urticaria has been noticed in association with CD and an improvement of symptoms was observed under gluten restriction (Humbert et al. 2006). However, a study of 80 patients with chronic urticaria failed to observe an increased incidence of CD compared to control patients (Gabrielli et al. 2005).

A potential relationship between psoriasis and gluten intolerance has been the focus of several studies including up to 28,958 patients with psoriasis (Ludvigsson et al. 2011). In many of these studies, an increased incidence of gluten intolerance has been observed. Possible explanations are as follows:

- Deficiency of vitamin D due to malabsorption caused by CD causes aggravation of psoriasis.

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- T cell reaction with accompanying increased IFNγ leads to a consecutive aggravation of psoriasis.
- Common genetic factors of psoriasis and CD.
- Immune-mediated incidents due to an increased intestinal permeability result in aggravation of psoriasis (Ludvigsson et al. 2011).

However, there are varying results concerning improvement of symptoms after gluten-free diet (Michaelsson et al. 2000; Zamani et al. 2010).

There are many more dermatological diseases, e.g., dermatomyositis, atopic eczema, pyoderma gangrenosum, and lupus erythematosus, for which in case reports an improvement of symptoms after starting a gluten-free diet has been described. The significance of these findings has yet to be determined.

Wheat Allergy

Wheat allergy is an IgE-mediated allergic disease characterized by anaphylactic reactions like urticaria, asthma, and gastrointestinal and cardiovascular symptoms. In individuals suffering from atopic eczema, it might cause worsening of the eczema. While gluten is a component of wheat and might also be detected by IgE antibodies, IgE-mediated allergic reactions should not be confused with the IgA- and sometimes IgG-mediated autoimmune reactions underlying DH and CD.

Summary

Dermatitis herpetiformis Duhring (DH) is the most important skin disease linked to gluten intolerance. DH is by many considered as a skin manifestation of celiac disease (CD).

Genetic, environmental, and autoimmune factors are involved in the pathophysiology of DH. Clinically excoriated grouped papulovesicles associated with intense pruritus may be observed mainly at the bilateral extensor surfaces, scalp, and buttocks. The diagnosis should be secured by the detection of granular-linear deposition of IgA along the dermo-epidermal junction zone by direct immunofluorescence. A gluten-free diet is the therapy of choice and may also prevent secondary diseases such as lymphoma. Because skin lesions dissolve several months to years after the initiation of a gluten-free diet, a symptomatic therapy with dapsone may be added.

Cross-References

▶ Urticaria

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Gold Contact Dermatitis

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Synonyms

Adverse reactions to gold; Cutaneous reactions to gold; Eczematous contact sensitivity to gold; Eczematous contact with gold

Definition

Gold contact dermatitis may be defined as an irritant or allergic inflammatory reaction of the skin to gold.

Introduction

Gold (Au) has been regarded as a relatively safe and inert material when in contact with the skin and mucosal membranes. Despite its extensive use, allergic contact dermatitis and stomatitis rarely occur.

Skin and mucosal exposure to gold happens as a result of contact with items made of pure metal, metal salts, alloys, and other compounds. However, to act as a hapten, gold must be ionized. The presence of dental gold and sensitization is statistically correlated (Möller 2010). Other sources, such as ear piercings and gold-plated cardiac stents, have also been shown to be a risk factor for gold hypersensitivity (Schalock et al. 2012).

Sources of Gold Exposure

The advantage of gold is derived from a variety of special properties. Gold is malleable, ductile, deflectable, resistant to corrosion, and a great conductor of electricity. Alloys with other metals, such as silver, copper, nickel, palladium, and zinc, are common to increase its strength and durability.

Gold is found mainly as an alloy in jewelry and in dentistry (crowns, bridges, dental fillings, orthodontic devices, etc.). It is also present in cosmetics, paintings, decorative applications in porcelain, photography, as well as in glassmaking. The most important industrial use of gold is in electronics manufacture (Lidén et al. 2011). In the medical practice, gold has been used for various purposes: to treat rheumatoid arthritis and certain cancers, in intracoronary stents, eyelid implants, acupuncture needles, herbal medicines, and diagnostically for which radioactive gold is used.

Gold as a Potential Sensitizer

The capacity of an elemental metal to sensitize or elicit contact allergy depends on the rate of formation of allergenic metal ions. The low incidence of contact dermatitis from gold is presumably due to

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its stability and low tendency to ionization. Gold use in jewelry has been demonstrated to induce sensitivity. This sensitivity is manifested as dermatitis. This reaction occurs due to the conversion of gold into a soluble form, as a result of the action of sweat amino acids, which form haptens that are absorbed through the skin. When gold penetrates through the epidermis, an eczematous contact reaction may be induced. It is mandatory to emphasize that gold dermatitis may be a "dermal type" of contact dermatitis (Rietschel and Fowlwer 2008). Direct contact with gold via piercing or wearing gold earrings may be associated with a trauma-induced inflammatory response, which can facilitate the development of hypersensitivity. The presence of allergens in this scenario could generate continuous solubilization of small amounts of gold into the tissue, allowing prolonged local antigen exposure. This suggests that the cellular response in the dermis with continuous antigen exposure is distinct from that characterized by contact sensitivity in the epidermis. Gold may be less stable in the dermis and thus ionize more. This implies that there is a relationship between ear piercing and gold allergy (Conde-Taboada et al. 2007; Mehta and Balachandran 2010).

A significant correlation between dental gold restorations and contact allergy to gold has been demonstrated, as well as between blood gold concentration and the amount of dental gold. Gold-plated stents were initially used due to the hypothesis that gold was an inert metal, thus less likely to cause inflammation or local reaction in vessels. Subsequent studies showed that gold exposure in cardiac stents is a strong risk factor for in-stent restenosis, especially in those with prior gold allergy (Schalock et al. 2012). Also, several occupational sources of exposure to metallic or ionized gold are known, but sensitization at workplaces seems to be infrequent (Möller 2010).

Clinical Picture

While sensitization does occur, there are few examples of classical contact dermatitis with the use of high-carat gold. In some instances, dermatitis from a ring is due to irritation from sweat retention, trauma, or accumulated detergents (Lidén et al. 2011). Allergic gold dermatitis may be shown as a persistent papular eruption characterized by minimal eczematous epidermal changes and by marked dermal involvement. This rare entity is characterized by nodules at sites of piercing with gold jewelry, which remain despite avoidance of further gold contact (Rietschel and Fowlwer 2008). The oral clinical manifestations of contact allergic response to dental gold can cause lichen planus on the buccal gingiva and mucosa (erythematous and erosive lesions), stomatitis, glossitis, and orofacial granulomatosis (Lidén et al. 2011).

Gold has been used for ocular prosthetics and eyelid implants. Patients with contact allergy to gold have developed localized dermatitis after receiving gold eyelid implants; the dermatitis resolved when the gold was removed (Björkner et al. 2008).

Systemic Contact Dermatitis

Gold therapy for rheumatic diseases may induce lichenoid eruptions and systemic contact dermatitis. Also, patients with allergy to gold can develop flare-up at previous sites of clinical contact dermatitis after systemic provocation with gold sodium thiomalate and when again exposed to gold during a patch test. Russell et al. reported three patients who developed lichenoid dermatitis after drinking a gold-containing alcoholic beverage (Russell et al. 1997). Recently, a woman taking a homeopathic medicine that contained gold for heart disease developed systemic contact dermatitis that disappeared after she discontinued use of the drug (Malinauskiene et al. 2013).

Occupational Gold Allergy

Exposure to soluble gold salts takes place in glass and porcelain gilding, photographic applications, gold smelting, and electronic industry.

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Airborne allergic contact dermatitis caused by gold is rare. Sporadic cases of occupational contact dermatitis from gold salts have been reported. The most frequent and typical manifestation of airborne allergic contact dermatitis is eyelid dermatitis, followed by involvement of the face, neck, and other exposed parts of the body (Giorgini et al. 2010). Potassium dicyanoaurate used in the electronics industry may cause allergic and irritant contact dermatitis (Rietschel and Fowlwer 2008).

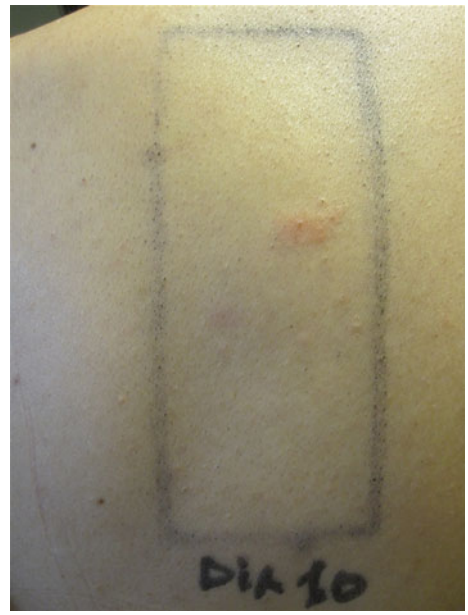
Patch Testing for Gold Allergy

Patch testing is the most reliable tool in diagnosing allergic contact dermatitis (ACD). Patch testing technique involves the application of test allergens under occlusion onto the skin of the upper back for 2 days. The first evaluation is generally performed between 15 and 60 min after patches are removed. The time of the second reading varies among different centers, but generally is on day four or five. (Fig. 1)

An additional reading at day seven may be useful to identify a small number of late, positive reactions.

Metallic gold (elemental) is not useful for patch testing, as it is poorly soluble and frequently yields false-negative results. Traditionally, gold trichloride (GTC), potassium dicyanoaurate, and gold sodium thiomalate (GSTM) were used to patch test for contact allergy to gold. A test solution of gold chloride is composed of gold in dilute hydrochloric acid. This acid compound has irritating properties with a risk of false-positive reactions. Gold trichloride was used by Kligman in a human maximization test and found to be a strong sensitizer. In recent years the gold salt sodium thiosulfate (GSTS), also known as sodium thiosulfatoaurate, has been reported to have a low frequency of irritant reactions compared with other gold salts. GSTS 0.5 % in petrolatum (pet.) is the appropriate antigen to demonstrate allergy to gold (Rietschel and Fowlwer 2008).

Gold Contact Dermatitis, Fig. 1 A vesicular allergic patch test reaction to GSTS 0.5 % pet (AllergEAZE ®)



Gold Contact Dermatitis, Fig. 2 GSTS 0.5 % pet: patch test positive at 10th day

Gold is a late-reacting allergen. It was found that patch test reactions to GSTS were often delayed, as positive reactions appeared 7–10 days after testing. This is a phenomenon similar to that observed with other allergens such as neomycin and corticosteroids (Fig. 2).

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Gold Contact Dermatitis, Fig. 3 GSTS 0.5 % pet: positive reaction 2 months after the patch test was removed

Occasionally, positive patch tests to GSTS may persist for weeks or months (Fig. 3) and gradually develop a nodular appearance due to the presence of the allergen in the dermis (Möller 2010).

Clinical Relevance

Gold allergy has been regarded as controversial since the relevance of a contact allergy to gold can be difficult to evaluate.

The bioavailability of gold sodium thiosulfate from gold-containing objects such as jewelry varies depending on factors such as perspiration, friction, or abrasive contact with titanium dioxide particles. Nedorost speculates that titanium dioxide in cosmetics (eye shadow, facial powder, foundation) and sunscreens may absorb gold released from hand jewelry that occasionally contacts facial skin and causes contact dermatitis on this area despite the absence of dermatitis under gold jewels worn on the hands (Nedorost and Wagman 2005).

Positive patch test reactions to gold without obvious clinical relevance are common. The variation in gold release may allow patients who tested positively to gold sodium thiosulfate to tolerate gold jewelry, whereas others present with eyelid or facial dermatitis that resolve upon discontinuation of gold use.

Conclusion

Due to the variation of gold release, patch testing with gold sodium thiosulfate is not recommended for the standard series, given the deficient understanding of the nature of the positive GSTS patch test. However, it should be considered for further investigation and when cutaneous allergy reactions to gold are suspected (Lidén et al. 2011).

Determining the relevance of gold sodium thiosulfate is challenging. Clinically, evaluation of patch test relevance is probably the most demanding aspect of patch test interpretation.

Cross-References

- ▶ Allergic Contact Dermatitis
- ▶ Contact Dermatitis Due to New Metals
- ▶ Eyes and Eyelid, Contact Allergic Reaction On

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H

Hairdressers' Occupational Skin Disease

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Definition

Hairdressers are exposed to multiple allergens and irritants such as ingredients in hair colors, permanent wave, and bleaching products (Table 1). Moreover, the profession comes along with a great amount of wet work. Therefore, hairdressing is one of the occupations with the highest incidence of occupational skin diseases (OSD) leading to a high frequency of worker disability (Frosch and Rustemeyer 2000; Sosted 2011; van der Walle 2000). The annual prevalence of hand eczema among hairdressers is around 13–22 %, but underreporting is common. Many hairdressers develop OSD very early in their career, frequently already during apprenticeship (Valks et al. 2005). Up to 40–50 % of hairdressers leave the profession, which is mainly linked to OSD (Lysdal et al. 2011). A history of atopic dermatitis is the greatest endogenous risk factor for the development of OSD in hairdressers (Leino et al. 1998; van der Walle 2000).

Occupational Skin Diseases (OSD)

The most common OSD in hairdressers is contact dermatitis, an inflammation of the epidermis and the outermost dermis due to exposure to irritants and/or allergens (Table 1). It is characterized by erythema, papules, blisters, and fissures in the acute phase and scaly, lichenified skin in the chronic phase. In the hairdressing trade, it is commonly found on the hands and forearms which are frequently exposed to hazardous substances. Initially, many hairdressers develop irritant contact dermatitis of the hands resulting in damage of the skin barrier. Subsequently, allergens penetrate the skin more easily causing allergic contact dermatitis, a delayed-type cell-mediated immune response (Bonneville et al. 2007). Therefore, hand eczema in hairdressers is often a combination of irritant and allergic contact dermatitis (Frosch and Rustemeyer 2000).

The hands of hairdressers are repetitively exposed to irritants (e.g., shampoos, permanent waving, and bleaching solutions) and wet work (e.g., washing hair, cutting wet hair, increased sweating by wearing protective gloves). Therefore, many hairdressers develop a gradually progressing irritant contact dermatitis (Frosch and Rustemeyer 2000). Typically, the interdigital webs as well as the second and third finger of the nondominant hand between which the wet hair is held while cutting are affected (Schwanitz and Uter 2000). The dermatitis may spread to the back of the hand and fingers, the wrist, and

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Hairdressers' Occupational Skin Disease, Table 1 Common irritants and allergens in the hairdressing trade

Compound	Irritant	Allergen
Bleaching		
Ammonium persulfate	+	+
Hydrogen peroxide	+	
Fragrances (selection)		
Cinnamal	+	+
Eugenol, Isoeugenol	+	+
Hydroxyisohexyl-3-cyclohexene carboxaldehyde (Lyral)	+	+
Gloves		
Thiurams		+
Dithiocarbamates		+
Mercaptobenzothiazoles		+
Latex		+
Hair dyes		
p-Phenylenediamine	+	+
Toluene-2,5-diamine	+	+
p-Aminophenol	+	+
m-Aminophenol	+	+
Resorcinol	+	+
Hydroquinone	+	+
Metal instruments (e.g., *scissors*)		
Nickel sulfate		+
Cobalt chloride		+
Permanent waving		
Ammonium thioglycolate	+	+
Glyceryl monothioglycolate	+	+
Cysteamine hydrochloride	+	+
Preservatives		
Chloroacetamide	+	+
Formaldehyde	+	+
Chlorocresol	+	+
Chloroxylenol	+	+
2-Bromo-2-nitropropane-1,3-diol	+	+
Methylchloroisothiazolinone/ methylisothiazolinone	+	+
Imidazolidinyl urea	+	+
Diazolidinyl urea	+	+
Parabens	+	+
Tenside		
Cocamidopropyl betaine	+	(+)

lower arms. Painful fissures and edema may worsen the clinical picture and impair the mobility of the fingers (van der Walle 2000). Friction and pressure caused by handling of various instruments (e.g., comb, scissors) adds to the irritant damage of the skin. Sometimes, localized hyperkeratosis (callosity) is induced by constant rubbing of the grips of scissors against the skin (van der Walle 2000).

Since hairdressers are exposed to many allergens at work (e.g., in hair colors, permanent waving and bleaching solutions, gloves), they also often develop allergic contact dermatitis which is mainly located on the hands and lower arms but may spread to other body sites. The face may be involved due to airborne exposure to allergens (airborne contact dermatitis). In hairdressers sensitized to hair colors, cutting of colored hair typically results in allergic contact dermatitis of the second and third finger of the serving hand as these fingers hold the hair during the cutting procedure (van der Walle 2000). The most important allergens in hairdressers are oxidative hair dyes and their intermediates such as *p*-phenylenediamine and toluene-2,5-diamine, ammonium persulfate and, with decreasing trend, glyceryl monothioglycolate (Frosch and Rustemeyer 2000; Sosted 2011). Most products in the hairdressing trade are perfumed and preserved. Therefore, sensitizations to fragrances and preservatives should be considered, too.

Besides irritant and allergic contact dermatitis, hairdressers may suffer from contact urticaria, which can be induced by latex gloves or ammonium persulfate used for bleaching. Usually, contact urticaria is confined to the area of exposure, but generalized urticaria can also occur, sometimes associated with extra-cutaneous symptoms (angioedema, rhinoconjunctivitis, asthma, circulatory dysregulation) (Sosted 2011).

A rather rare OSD in hairdressers is interdigital pilonidal sinus caused by penetration of freshly cut hair into the skin in the interdigital spaces of the hands with subsequent foreign body reaction (Frosch and Rustemeyer 2000).

Causative Factors

Washing Hair

Water removes epidermal lipids resulting in dry skin with impaired epidermal barrier function

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(van der Walle 2000). In addition, detergents in shampoos and conditioners irritate the skin. The amphoteric surfactant cocamidopropyl betaine commonly used in shampoos and liquid soaps is a well-known irritant, only rarely causing allergic contact dermatitis. Patch test reactions are difficult to interpret due to irritant reactions (de Groot et al. 1995; van der Walle 2000). Moreover, shampoos may contain fragrances and preservatives (e.g., chloro-methyl-isothiazolone/methyl-isothiazolone (CMI/MI), formaldehyde releasers) with irritant and/or allergic potential.

Cutting Hair

Cutting is done with the dominant hand holding the scissors while the serving hand guides the comb or presents a row of hair to the scissors by squeezing hair between the second and third finger. The skin contact to moist and wet hair while cutting is considered as wet work resulting in chronic skin damage. Handling of instruments (e.g., scissors) may contribute to the skin disease by repetitive frictional forces (van der Walle 2000).

Permanent Waving

During the perming process disulfide linkages in the keratin filament are broken by reducing agents, thus enabling the rearrangement of the keratin filament. After winding, new disulfide linkages are built and fixed by oxidation creating a (semi)permanent wave or curl. Glyceryl monothioglycolate (GMTG) is a common ingredient in acidic permanent wave products (pH 5–6) with a strong allergenic potential (van der Walle 2000). Therefore, in Germany, producers of professional hair cosmetics agreed in 1995 with the organization of hairdressers' employers to stop the use of GMTG in perm wave solutions. This was followed by national regulations resulting in a declining prevalence of newly acquired sensitizations to GMTG (Uter et al. 2007). Nowadays, in many countries alkaline permanent wave products (pH 8–9) are preferred because they do not contain GMTG (van der Walle 2000). Their active ingredient is ammonium thioglycolate (ATG) which only rarely causes allergic contact dermatitis (Uter et al. 2007). Cysteamine hydrochloride is another replacement for GMTG with low allergenic potential. For oxidation hydrogen peroxide is usually used which is a potent irritant and only rarely causes allergic contact dermatitis (Kanerva et al. 1998).

Coloring Hair

For permanent hair dyeing, oxidative dyes and their intermediates, such as *p*-phenylenediamine (PPD), toluene-2,5-diamine (PTD), *p*-aminophenol, and couplers (e.g., *m*-aminophenol, resorcinol, 1-naphthol, hydroquinone), are used (van der Walle 2000). In addition, further oxidants such as hydrogen peroxide are a common ingredient of oxidative hair dyes. Hair dyes and their intermediates are the major allergens causing allergic contact dermatitis in hairdressers (Valks et al. 2005). Skin contact is possible during the coloring procedure, while cutting newly dyed hair and also from contaminated surfaces (Sosted 2011). Within the European Union the maximal concentration of PPD allowed in hair coloring products is 6 % (Annex III to 76/768/EEC). PPD and PTD belong to the most common causes of allergic contact dermatitis in hairdressers and their customers. Among hairdressers around 18 % and 19 % are sensitized to PPD and PTD, respectively (Uter et al. 2007). Cross-reaction between the different para-amino dyes is a common problem in sensitized individuals. Pyrogallol is used as a coupler in hair dyes. In Europe it was banned in 1992 by the Cosmetic Directive due to its allergenic potential. Hydroquinone and resorcinol are couplers in hair dyes with a rather low allergenic capacity. Monoethanolamine (MEA) has been mainly used in cooling fluids but can be found in hair coloring products to regulate the pH. Sensitization rates to MEA have been low but are on the increase (Sosted 2011).

Bleaching Hair

For bleaching hydrogen peroxide is applied. Hydrogen peroxide is a strong irritant only rarely causing allergic contact dermatitis (Kanerva et al. 1998). Almost every bleaching and highlighting product contains additionally sodium, potassium, or ammonium persulfate to increase the effect of hydrogen peroxide. Persulfates may induce both

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allergic contact dermatitis and immediate-type hypersensitivity reactions such as asthma. Some companies offer bleaching products consisting of granulates instead of dusts in order to decrease the number of bronchial reactions. However, still many hairdressers suffer from airway symptoms while bleaching (Sosted 2011).

Styling Hair

Hot air from the hair dryer during styling procedures may cause dehydration of the stratum corneum (Frosch and Rustemeyer 2000). Styling products such as sprays, mousses, and gels may contain preservatives (e.g., CMI/MI) and fragrances.

Gloves

Protective gloves are worn by hairdressers to prevent direct skin contact to hair dyes, bleaching agents, or permanent wave products. However, gloves often contain allergens themselves (e.g., latex, thiurams, dithiocarbamates, and mercaptobenzothiazoles) (Sosted 2011). In addition, the occlusive effect may contribute to the development of irritant and subsequently allergic contact dermatitis (van der Walle 2000).

Handling Instruments

Instruments (e.g., combs, scissors) may cause friction and pressure resulting in irritant contact dermatitis or callosities. Nowadays, scissors are primarily made from stainless steel and the grips are covered with plastic. Therefore, occupational allergic contact dermatitis due to nickel or cobalt is not common among hairdressers anymore. The high prevalence of sensitization to nickel in hairdressers is rather due to a high percentage of women in this profession and their preference of ear piercing and wearing of jewelry at young ages (Frosch and Rustemeyer 2000). The newly implemented European Union Nickel Directive may decrease the overall exposure to nickel and related sensitization in Europe in the future.

Cleaning Procedures

Hairdressers may also perform cleaning of surfaces, floors, and instruments using various cleaning products which may contain disinfectants (e.g., formaldehyde, glutaraldehyde), fragrances, preservatives, and detergents causing irritant and/or allergic contact dermatitis (Flyvholm 1993).

Diagnostics

The diagnosis must be based on history, clinical findings, and the result of patch testing (Frosch and Rustemeyer 2000). For patch testing, the standard series and the supplementary series for hairdressers should be used (Frosch and Rustemeyer 2000; Sosted 2011). Materials from the workplace should be tested if the suspicion of a missed allergen is raised after negative tests. The interpretation of the results should be done with respect to relevance and potential false-positive or false-negative results. When nickel allergic hairdressers present with hand eczema, their work tools should be investigated for nickel release with the DMGO test if occupational nickel exposure is suspected (Frosch and Rustemeyer 2000).

If hairdressers suffer from occupational rhinitis or asthma, a prick test should be performed with ammonium persulfate and latex (Frosch and Rustemeyer 2000).

Management and Prevention

For the management and prevention of OSD in hairdressers, the expertise of occupational health and safety professionals and dermatologists is required (van der Walle 2000). Medical treatment of contact dermatitis mainly includes topical corticosteroids and UV light therapy. The implementation of prevention measures are of utmost importance. To prevent OSD in hairdressers or to achieve a long-lasting improvement in those who already suffer from OSD, awareness of potential risks should be raised and the application of protective measures encouraged (Wulfhorst et al. 2011). Skin-damaging factors should be eliminated or avoided. This can be achieved, e.g., by spreading

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wet work among multiple employees to minimize the individual exposure. A regular switch between moist and dry activities should be arranged in the workflow. Protective gloves should be worn when preparing and applying hairdressing chemicals (dyes, bleaching agents, permanent wave products) as well as when in contact with water (washing) or wet hair. Single-use gloves made from nitrile rubber or polyvinyl chloride are appropriate with adequate normation. For individuals with sensitizations to rubber accelerators (such as mercaptobenzothiazoles, dithiocarbamates, thiurams), special accelerator-free protective gloves are available (Sosted 2011; Wulfhorst et al. 2011). Wearing gloves often leads to a blockade of moisture and heat. To reduce this, cotton under-gloves can be worn which should be changed after becoming moist. In the hairdressing trade, wearing gloves when cutting hair is not well accepted, as this is often associated with reduced fine motor skills. In this case, the client's hair should be cut before coloring to avoid contact with hair dyes. Emollients and skin protection creams should be applied regularly on the hands to improve the epidermal barrier (Wulfhorst et al. 2011).

Preferably products containing relevant allergens should be replaced by others. However, this is often not possible as some of the most important allergens in the hairdressing trade are ubiquitous in hair products.

Good practical advice on self-management is available from hairdressing organizations and statutory accident insurances. In some countries (e.g., Germany) combined preventive measures based on health education and dermatological treatment are offered to patients with OSD which has been proven successful in hairdressers (Wulfhorst et al. 2010).

Cross-References

- ▶ Allergic Contact Dermatitis
- ▶ Hairdressers' Occupational Skin Disease
- ▶ Sensitization and Allergy to Natural Rubber Latex

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Herbal Remedies

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Synonyms

Botanical medicine; Complementary alternative medicine; Herbal supplements; Natural medicine

Definition

Herbal medicine, a branch of complementary alternative medicine (CAM), is sold without a prescription to promote and support overall health. The documented use of herbal therapy dates back to over 5,000 years ago. By the Middle Ages, over 1,000 plants were cataloged for their medicinal purposes (NCCAM 2008). In 2007, the CDC National Health Statistics Report estimated approximately 17.7 % of the US population utilizes herbal medicine. The most common were fish oil, glucosamine, and *Echinacea* (NCCAM 2008). Approximately 35.9 million Americans suffer from seasonal/perennial allergies (Nathan et al. 1997). It is important for consumers and healthcare practitioners alike to understand herbal products are not regulated by the Food and Drug Administration (FDA), as their safety and efficacy have not been thoroughly evaluated. This entry will review herbal medications commonly used by patients with allergies, and will discuss their effectiveness.

Butterbur (*Petasites hybridus*)

Butterbur (*Petasites hybridus*), also known as Blatterdock, Bog Rhubarb, and Exwort, is a plant indigenous to Europe, southwest Asia, and north Africa (Schapowal 2002). The root, rhizome, and leaves are used to extract the chemicals, petasin and isopetasin, for its medicinal purposes. This herbal preparation is primarily used for migraine prophylaxis; however, studies during the 1990s demonstrated the role of *Petasites hybridus* in inhibiting leukotriene synthesis, and may have potential in the treatment of allergic rhinitis (Brune et al. 1993).

Butterbur Mechanism of Action: In allergic rhinitis, histamine, cysteinyl leukotrienes, and LTB_4 are the primary mediators of allergic responses (Thomet et al. 2002). In vitro studies suggest that petasins (including petasol butenoate) in butterbur inhibit the binding of histamine at the H1 receptors, attenuate leukotriene synthesis, and reduced pro-inflammatory cytokine, IL-8 (Dumitru et al. 2011).

Butterbur Clinical Trials: Studies with butterbur have demonstrated efficacy in randomized clinical trials for allergic rhinitis.

A randomized, double-blind, parallel group study compared the effectiveness of an antihistamine (cetirizine 10 mg daily) to butterbur (8-mg butterbur leaf extract Tesalin® four times daily) in 125 participants (Schapowal 2002). Tesalin® is a complex of petasin, isopetasin, and neopetasin as the primary active ingredients and standardized to 8 mg of petasin per tablet. Endpoints were measured on a medical outcome health survey questionnaire (SF-36), and the clinical global impression scale. Each treatment group demonstrated similar efficacy on both scales, and exhibited minimal side effects. Both treatment groups experienced a similar incidence of adverse effects, 17 % (11/64) in the cetirizine group and 16 % (10/61) in the butterbur group. Sixty-six percent of patients who reported adverse effects in the cetirizine group were related to the sedating antihistamine effects: fatigue (n = 6) and drowsiness (n = 2). With the butterbur group, no single adverse effect could be considered attributable because only one or two participants experienced each reported adverse event.

A 2004 study compared the safety and efficacy of butterbur extract (Tesalin®) in 186 patients

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with intermittent allergic rhinitis by randomizing patients to either 8 mg three times daily, 8 mg twice daily, or placebo (one tablet three times daily) for 2 weeks (Schapowal 2004). The primary outcome for efficacy was measuring change from baseline in four main symptoms (rhinorrhea, nasal congestion, rhinitis, and sneezing) using a visual analog scale. Results showed that the higher dose butterbur extract was superior to placebo in terms of rhinorrhea. The lower dose of butterbur extract was superior to placebo for relieving the symptoms of sneezing and rhinitis ($p < 0.001$). In addition, the higher dose of butterbur extract was superior to the lower dose for the symptoms of rhinitis nose or excessive lacrimation ($p < 0.02$).

Schapowal et al. also reported, the most common side effect of butterbur extract was gastrointestinal (GI) discomfort in three patients in the high dose butterbur group one report of GI discomfort in the low dose butterbur group, and three in the placebo group. Other adverse effects reported in both the placebo and butterbur groups were nausea (two patients in higher dose butterbur group and one in placebo) and skin rash (one patient in both higher dose of butterbur and placebo) (Schapowal 2004).

A randomized, double-blind, placebo-controlled trial compared whole root butterbur extract 50 mg twice daily (Petaforce®) to fexofenadine 180 mg daily and to placebo (Lee et al. 2004). Petaforce® contains 7.5 mg of petasin and isopetasin per 50-mg tablet. Data from this study demonstrated that both butterbur and fexofenadine were equally efficacious in alleviating nasal symptoms and also diminished nasal response to adenosine monophosphate (AMP) in patients with perennial allergic rhinitis.

A study compared butterbur 50 mg twice a day to fexofenadine 180 mg daily and montelukast 10 mg daily in the setting of allergic skin reactions. Both fexofenadine and montelukast decreased wheal and flare responses, whereas butterbur did not demonstrate a significant response (Jackson et al. 2004).

Butterbur Safety: A concern with butterbur is the potential for hepatotoxicity. Butterbur root contains pyrrolizidine alkaloids, which have demonstrated hepatotoxicity and carcinogenesis (Chojkier 2003). Petaforce® has been discontinued by the manufacturer; however, Tesalin® is still commercially available in Switzerland, where it is registered as prescription only.

Butterbur Drug Interactions: Pyrrolizidine alkaloids are metabolized by CYP 3A4 metabolic enzymes to pyrroles which have demonstrated toxicity in humans (Chojkier 2003). Drugs, such as rifampin, phenytoin, and phenobarbital, and St. John's Wort are inducers of CYP 3A4. These agents have the potential to enhance toxicity by converting pyrrolizidine into pyrroles.

Milk Thistle (*Silybum marianum*)

Milk thistle (*Silybum marianum*) was named for the milky white substance that is released when the leaves are broken. The names "Mary Thistle" and "Holy Thistle" are derived from the legend that the white fluid produced was the Virgin Mary's milk. It is also known as Silybum and Silymarin. Common use of this herb is in hepatic diseases including hepatitis, cirrhosis, and chronic inflammatory liver disease but is now being investigated in allergic rhinitis setting.

Milk thistle Mechanism of Action: The mechanism of action of milk thistle for allergic rhinitis has not been elucidated. Evidence in concordance with a potential for hepatoprotection due to the attenuation of oxidative stress, milk thistle may have a role in allergic rhinitis because environmental oxidative stress contributes to the pathophysiology of allergic rhinitis (Pradeep et al. 2007).

Milk Thistle Clinical Trials: One recent study compared the efficacy of milk thistle extract (140 mg three times daily) versus cetirizine (10 mg daily) for 1 month in 60 patients. Results were measured on the Sino-Nasal Outcomes Test 20. Milk thistle had a statistically significant improvement in clinical symptoms compared to cetirizine (9.23 ± 5.14 vs. 2.20 ± 2.69; $p < 0.001$) (Bakhshaee et al. 2011).

Milk Thistle Safety: According to a systematic review and meta-analysis, including 14 clinical

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trials, GI symptoms were the most common adverse effect with the frequency ranging from 2 % to 10 % ; however, this was indiscernible compared to placebo (Jacobs et al. 2002).

Milk Thistle Drug Interactions: Evidence suggesting that milk thistle affects the cytochrome P450 enzymes 2C9 and 3A4 are conflicting and unlikely at the recommended maximum daily dose (Sridar et al. 2004). Regardless, because of the potential, caution is advised during concomitant administration of milk thistle and medications that are 2C9 inhibitors (e.g., warfarin, diltiazem and verapamil) or 3A4 inhibitors (e.g., amiodarone, clarithromycin, and ritonovir). There is potential for milk thistle to interact with drugs that undergo Phase II conjugation. Milk thistle has been shown to inhibit hepatic UDP-glucuronosyltransferases (UGT 1A1); therefore, the potential exists for milk thistle to interact with drugs that undergo this pathway of metabolism (e.g. estradiol, buprenorphine and irinotecan) (Sridar et al. 2004).

Pycnogenol

Pycnogenol is a blend of procyanidins extracted from the French Maritime Pine Bark (*Pinus pinaster or Pinus maritima*) (Packer et al. 1999). It is also known as condensed Tannins, French Marine Pine Bark Extract, *Pinus pinaster*, *Pinus maritima*, Leucoanthocyanidins, Maritime Bark Extract, Oligomeric Proanthocyanidins (OPCs), Pine Bark Extract, Procyandiol Oligomers (PCO), Procyanidin Oligomers, Procyanodolic Oligomers, and Pygenol. The term "Pycnogenols" was originally designed to describe flavonoids composed of flavan-3-ol derivatives; however, it is now the registered trademark name for the French Maritime Pine Bark extract blend (Grosse Duweler and Rohdewald 2000). Although Pycnogenol's exact chemical composition is not completely known, it is composed of multiple active ingredients including flavonoid monomers, condensed procyanidins, phenolic acids, their glucosides, and glucose esters. Pycnogenol is used to treat multiple diseases; however, this entry will focus on the treatment of allergic rhinitis.

Pycnogenol Mechanism of Action: Pycnogenol is composed of proanthocyanidins, condensed flavonoids, which has anti-allergic, anti-inflammatory, antiviral, and antioxidant properties (Packer et al. 1999). It has been proved to reduce serum and urinary leukotrienes LTC_4, D_4, and E_4 (Lau et al. 2004). These properties make Pycnogenol a potential candidate for treating allergic rhinitis and asthma.

Leukotrienes bind to cysteinyl leukotriene receptors, ($CysLT_1$) in the nasal mucosa and result in the early and late phase reactions associated with allergic rhinitis, including increased sinus congestion, leading to nasal airway resistance and obstruction. Pycnogenol may benefit allergic rhinitis by reducing the number of leukotrienes available to bind to $CysLT_1$.

Pycnogenol Clinical Trials: Limited, well-designed evidence evaluating Pycnogenol allergic rhinitis exists. A small randomized, double-blinded, placebo-controlled trial evaluated Pycnogenol's effects in eye and nasal allergic rhinitis symptoms (Wilson et al. 2010). The Pycnogenol dose used was 50 mg twice daily. Although no statistically significant effects were observed, Pycnogenol administered at least 5 weeks prior to allergy season demonstrated a nonsignificant trend toward improvement in eye and nasal symptoms.

Pycnogenol Safety: Wilson et al reported no significant differences between Pycnogenol and placebo (Wilson et al. 2010). Common side effects observed in both arms were headache, vertigo, common cold, and xerostomia; however, the frequencies of these were not reported. Pycnogenol has been used safely for 6 months in doses of 150 mg/day for the treatment of metabolic syndrome (Belcaro et al. 2013). In children with asthma, 1 mg/lb has been used safely in ages 6–18 for up to 3 months (Lau et al. 2004).

Pregnancy and lactation: Insufficient information available, avoid use.

Pycnogenol Drug Interactions: Pycnogenol has demonstrated to have immune-stimulating activity and can theoretically interact with medications and disease states (Rohdewald 2002). Pycnogenol may interfere with immunosuppressant medications including tacrolimus, corticosteroids, azathioprine, and others; therefore, it

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should not be administered concurrently. Caution should be exercised in patients with autoimmune disorders, including multiple sclerosis, systemic lupus erythematosus, rheumatoid arthritis, and other autoimmune disorders.

Conclusion

Due to CAM's (including herbal products) over-the-counter status and widespread availability, practitioners should be cognizant of their patient's use of these products. Being aware of the herbal product's safety and efficacy can help treatment.

FDA-approved medications undergo a comprehensive drug development process which includes preclinical testing and three phases of large-scale randomized clinical trials to elucidate the safety and efficacy of a medication. This process, from discovery to market approval, can take up to 16 years (unless expedited due to severity of disease). If a drug is discovered to be unsafe and/or ineffective during this process, the FDA will recommend the medication not to be brought to market by the pharmaceutical manufacturer, which is invariably followed. A drug's safety and efficacy profile is extended even during post-marketing surveillance, phase 4 clinical trials, and other clinical trials, which continue to monitor a drug's safety and efficacy. Additionally, pharmaceutical manufacturers must comply with current Good Manufacturing Process (cGMP), which is enforced by the FDA. cGMP ensures high-quality standards in the manufacturing process to maintain proper stability and sterility.

CAM is not regulated by the FDA and thus may not meet the standards set by the FDA. Regardless of the products reviewed in this entry, the trials are not large-scale in nature, and clinical recommendations purporting their use cannot be made. Because of these limitations, patients who consume CAM may be at risk for several clinical scenarios, including:

- The patient consumes CAM in place of the conventional medication, and is at risk for lack of efficacy and/or safety in the treatment of his/her allergic condition.
- The patient consumes CAM in place of the conventional medication, and untoward or previously unrealized reactions occur within the patient.
- The patient consumes CAM concomitantly with the conventional medication and known (or unknown) drug interactions may affect the CAM and/or the conventional medication in a way that can cause toxicity or ineffectiveness of either medication.

FDA-approved medications are not without risk; however, because of the exhaustive FDA approval process and post-marketing surveillance, the safety and drug interaction risk profile is generally known. If safety becomes an issue with an FDA-approved drug, it may be given a boxed warning, or removed from the market. Notable examples in the treatment of allergic diseases include antihistamines astemizole (Hismanal®) and terfenadine (Seldane®), both of which caused Torsades des Pointes due to drug interactions with inhibitors of P450 3A4 (Huang et al. 2006).

All health care professionals need to be aware of their patients who may be taking CAM. Finding out the patient who is taking CAM can be more rigorous especially during the interview, as the patient may be quite reserved because of the fear of being admonished for such use. Once the determination is made, physicians and health care professionals can have a more open dialogue with their patients about the use of CAM, be it beneficial or detrimental to the patient.

Cross-References

▶ Allergen Immunotherapy, Overview
▶ Immunotherapy for Asthma

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Homeopathy in the Treatment of Allergic Diseases

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Synonyms

Alternative medicine; Classical homeopathy; Clinical homeopathy; Complex homeopathy; Homeopath; Homeopathy medicine; Isopathy

Homeopathy, Definition

Homeopathy is a philosophy of medicine that was originated in the 1790s by the German physician, Christian Friedrich Samuel Hahnemann. His first published paper was in 1796, and was followed up with a textbook explaining his rationale in 1810 "The Organon of the Healing Art." The principle of homeopathy is "like treats like" in which substances of a said ailment are thought to be isolated, purified, and then diluted. Each dilution must be shaken vigorously. The dilution is based on factors of 100, and is called the Hahnemann or "C" (centesimal) scale. For example, a 2C dilution would require one part of substance in 100 parts water. Then, one part of this first dilution is another 100 parts water.

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The original mass and volume are not specified. However, if one mole is assumed, then using the dilution factor of 2C, then the equivalent will be a ratio of 1:10,000, or 1×10^{-4} (McCarney et al. 2004; Ballard 2000).

More modern dilution factors are by a decimal scale, designated by "X." This scale's dilution is by a factor of 10 by each stage. Thus, the above example of 2C would be 4X.

Example Dilutions of Homeopathy Preparations

A common dilution proposed by Dr. Hahnemann for many diseases was 30C. This is equivalent to a 1×10^{-60}. This is equivalent to one part in one trillion trillion trillion trillion trillion ($1{:}1 \times 10^{60}$). To conceptualize the infinitesimal concentration, consider the Earth has approximately 1.26×10^{21} l of water, which is equal to 7×10^{22} moles of water. By Avogadro's Number, 7×10^{22} moles of water has 4.22×10^{46} molecules. With the ratio of 30C being $1{:}1 \times 10^{60}$ as a concentration, and thus would be one molecule of substance in enough water for 23.7 trillion earths.

A current example of homeopathy medication includes the recent popularity of Oscillococcinum (Oscillo®). The product contains portions from the heart and liver of a duck (Anas barbariae hepatis et cordis extractum) with the dilution factor of 200C (400X, or $1{:}1 \times 10^{400}$). The concentrations involved would suggest there is not enough matter in the observable universe to contain a single molecule of Anas barbariae hepatis et cordis extractum (Park 2010).

Those who study and practice in homeopathy suggest it is not the physical form of the extract of the substance that is important, but it is the energy associated with it, and its influence on the water's "memory" that surrounded the original substance (or the water retains the "spirit" of the substance). It is also believed that the more dilute the preparation, the more potent it becomes. There is no evidence in the physical sciences to support these ideas.

Homeopathy and the FDCA

Because homeopathy was included in the Federal Food, Drug, and Cosmetic Act (FDCA) of 1938, and recognizes as official the Homeopathic Pharmacopeia of the United States (HPUS). Homeopathic medications follow a regulatory nature similar to that of over-the-counter products (Borenman and Field 2006).

Claritose®

Claritose® is an a homeopathy medication (http://www.claritose.com/), touted to treat the symptoms allergies, including: red, itchy and watery eyes, sneezing, coughing, sinus, nasal congestion, headaches, sore throat, hoarseness, deep itch in nose and throat, light sensitivity, among others. Claritose® lists ten ingredients, which are included in Table 1. It should also be noted that each ingredient has multiple claims, and are not limited to the treatment of allergic diseases.

The website states this homeopathic medication is prepared by 10X, 30X, and LM1 dilutions. Upon inquiry with the proprietor's (HelloLife®) call center, it was stated that the sequence of dilutions was to increase duration of action and potency. If the dilutions are prepared serially, then the ratio of said active ingredient to water would be one part in 2×10^{45} parts of water.

There is no available published literature on the effectiveness of Claritose® for allergic rhinitis. The company's website provides a white paper, which cites three clinical trials. These trials focused on the effectiveness of homeopathy on the common cold, not allergic rhinitis.

Subclasses of Homeopathy

As stated previously, homeopathy's core tenet is "like treating like." However, homeopathy may be divided up into other subclasses. These include:

Classical homeopathy: utilizing one homeopathic ingredient for a condition (O'Mathúna and Horgan 2005)

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Homeopathy in the Treatment of Allergic Diseases, Table 1

Homeopathic remedy name	Source	Claimed use
Allium Cepa	Garden onion	Nose ailments: Sneezing, especially when entering a warm room. Copious, watery, and extremely acrid discharge. Feeling of a lump at root of nose. Hay-fever. Fluent coryza with headache, cough, and hoarseness. Polypus.
Ambrosia Artemisiaefolia	Common Ragweed	A remedy for hay-fever, lachrymation and intolerable itching of the eye-lids. Nose ailments: Watery coryza; sneezing; watery discharge. Nosebleed. Stuffed up feeling of nose and head. Irritation of trachea and bronchial tubes, with asthmatic attacks (Aral; Eucalypt).
Arsenicum Album	Arsenic trioxide	Arsenicum album treatment for Nose ailments: Thin, watery, excoriating discharge. Nose feels stopped up. Sneezing without relief. Hay-fever and coryza; worse in open air; better indoors. Burning and bleeding. Acne of nose. Lupus.
Arundo Muritanica	Reed grass	Arundo mauritanica treatment for Nose ailments: Hay-fever begins with burning and itching of palate and conjunctiva. Annoying itching in the nostrils and roof of the mouth (Wyethia). Coryza; loss of smell (Nat mur). Sneezing, itching of nostrils.
Arum Triphyllum	Flowering plant, noted to have irritating properties by botanists	Arum triphyllum treatment for Nose ailments: Soreness of nostrils. Acrid, excoriating discharge, producing raw sores. Nose obstructed; must breathe through mouth. Boring in the nose. Coryza; discharge blood-streaked, watery. Nose completely stopped, with fluent, acrid discharge. Hay-fever, with pain over root of nose. Large scabs high up on right side of nose. Face feels chapped, as if from cold wind; feels hot. Constant picking at nose until it bleeds.
Euphrasia Officinalis	Small flowering plant	Euphrasia officinalis treatment for Nose ailments: Profuse, fluent coryza, with violent cough and abundant expectoration. Euphrasia officinalis treatment for Eyes ailments: Catarrhal conjunctivitis; discharge of acrid matter. The eyes water all the time. Acrid lachrymation; bland coryza (Opposite: Cepa). Discharge thick and excoriating (Mercur thin and acrid). Burning and swelling of the lids. Frequent inclination to blink. Free discharge of acrid matter. Sticky mucus on cornea; must wink to remove it. Pressure in eyes. Little blisters on cornea. Opacities. Rheumatic iritis. Ptosis (Gels; Caust).
Naphthalinum	[source is] naphthalene – a coal tar	Naphthalinum treatment for Respiratory ailments: Sneezing; eyes inflamed; painful; head hot. Hay-fever. Spasmodic asthma; better in open air. Soreness in chest and stomach; must loosen clothing. Dyspnea and sighing inspiration. Emphysema in the aged with asthma. Whooping-cough, long and continued paroxysms of coughing, unable to get a respiration. Acute laryngo-tracheitis. Bronchitis when the spasmodic element is associated with tenacious expectoration and oppression (Cartier).
Natrum Muriaticum	Sodium Chloride	Violent, fluent coryza, lasting from 1 to 3 days, then changing into stoppage of nose, making breathing difficult. Discharge thin and watery, like raw white of egg. Violent sneezing coryza. Infallible for stopping a cold commencing with sneezing. Use thirtieth potency. Loss of smell and taste. Internal soreness of nose. Dryness.

(*continued*)

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Homeopathy in the Treatment of Allergic Diseases, Table 1 (continued)

Homeopathic remedy name	Source	Claimed use
Sabadilla	Seeds of *Schoenocaulon officinale* plant (which contains steroidal pesticides (J Agric Food Chem 1996 44 149))	Spasmodic sneezing, with running nose. Coryza, with severe frontal pains and redness of eyes and lachrymation. Copious, watery, nasal discharge.
Wyethia Helenioides	from Sunflower family (a.k.a. gray mule, s ears)	Has marked effects on the throat, and has proven an excellent remedy in pharyngitis, especially the follicular form. Irritable throats of singers and public speakers. Useful also in hemorrhoids. Hay-fever symptoms; itching in posterior nares.

Source: www.webhomeopath.com

Complex homeopathy: utilizing fixed combinations of remedies (O'Mathúna and Horgan 2005)

Clinical homeopathy: utilizing the same remedy for people with similar conditions (O'Mathúna and Horgan 2005)

Isopathy: homeopathically prepared substances that are responsible for the disease itself (i.e., allergens such as pollen), the resultant homeopathic drug is called an "isode" (O'Mathúna and Horgan 2005; Kim et al. 2005)

Clinical Trials Involving Homeopathy

A group set out to compare classical homeopathy to conventional [western] treatment for allergic disease in a prospective observational cohort study (Gründling et al. 2012). Participants had to be at least 9 years of age, and exhibit symptoms consistent with the diagnosis of neurodermatitis, allergic rhinitis, allergic conjunctivitis, and bronchial asthma. Patients had to have persisting disease, and be naïve to classical homeopathy. Patients were seen by their physician, completed a questionnaire, and initiated on treatment. Treatment lasted 2 to 16 weeks, depending on treatment course, and was completed with a follow-up questionnaire. Although treatment with homeopathy included a variety of sources (mineral, vegetable, plant, and pathogen based), the specific ingredients were not listed. Fifty-three percent of patients were concomitantly taking conventional therapy with medications including antihistamines, inhaled and topical corticosteroids, bronchodilators, and leukotriene modifiers. Forty participants completed the study, those who were taking concomitant conventional therapy, 13 (62 %) were able to discontinue, while another 8 (38 %) were able to reduce their conventional medication dosages. Approximately 98% were satisfied with their homeopathic treatment, and continued after the completion of the study. Several limitations to this study were evident, including lack of clarity and description of adherence to the homeopathy and specific type of treatment, respectively, whether or not participants decided to initiate other means of conventional therapy, variability in the treatment period, and clear definition on allergic disease phenotypes.

A study employing the homeopathy concept of isopathy was conducted to investigate if the treatment was better than placebo for the treatment of seasonal allergic rhinitis. This was a randomized parallel placebo controlled trial and was conducted with homeopathic isopathy preparations compared to placebo. The investigators utilized concentrations which are much more similar to concentrations seen in allergy immunotherapy, which were denoted as 6X (micromolar) as compared to commonly seen dilutions of homeopathy ($1{:}1 \times 10^{60}$). Treatment was given as two sprays sublingually three times daily, which may arguably be similar to sublingual immunotherapy. Some of the components for the isopathy therapy were *Betula verrucosa* (birch), *Cynodon dactylon* (Bermuda grass), and *Ambrosia psilostachya* (ragweed). Forty participants underwent randomization to receive

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either homeopathic treatment or placebo for 4 weeks. Participants completed a medical examination and questionnaire evaluation at the baseline and at 4 weeks, with weekly phone calls to determine progress and adherence to the regimen. Thirty-four participants completed the trial and compared to baseline, the homeopathy treatment demonstrated significant improvements when reporting on the Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ), whereas placebo did not. Additionally, the authors claim that the homeopathic treatment was superior to placebo ($p < 0.05$). This trial has come under scrutiny, as detractors suggest the statistical methods were unsound (O'Mathúna and Horgan 2005).

Clearly, there are strong opinions for proponents of homeopathy, and those who oppose the philosophy. There have been petitions to the FDA to cease in the recognition of homeopathy (Skolnick 1994). The argument has been made that homeopathy does not treat specific disease states, but treating "people who are ill" (Skolnick 1994). This lends to the notion of placebo-effect. Generally, those trials that demonstrate benefit of homeopathy have questionable study design and statistical analyses. To date there are no large-scale randomized controlled clinical trials that demonstrate the benefit of homeopathy as compared to conventional treatment for allergic diseases.

Nambudripad's Allergy Elimination Technique (NAET) Therapy

Nambudripad's Allergy Elimination Technique (NAET) Therapy. NAET was "discovered" in 1983 by Devi S. Nambudripad, who combines acupressure, muscle response testing (kinesiology), and other methods to eliminate allergies (http://www.naet.com/subscribers/what.html) (Teuber and Porch-Curren 2003). The procedure is described as several steps. First the patient undergoes a session of acupuncture or acupressure in order to "drain energy blockages" while the patient is holding a vial of the causative allergen. Next, a brief waiting period (minutes) for the patient. Then the patient undergoes applied kinesiology, as the patient undergoes response testing. If the patient is "strong" to the allergen, the patient (Step 3) must avoid the allergen over the course of the next day. After this avoidance period, the patient is retested in the same manner until the allergy is eliminated.

There is one case report in the literature that reports success in a 3-year-old child with intolerances/allergy to milk, sugar, egg white, pork, and other foods. Allergy was determined by elimination challenge test, and ingestion of said foods caused eczema on the upper back 48 h after consumption. One allergy was treated per session, and after seven sessions (4 weeks), the foods that caused allergies were reintroduced without consequence. Of note, the patient was the author's child (Terwee 2008).

There are a large magnitude of internet websites that provide testimonial to NAET therapy. To date, there are no clinical trials providing evidence to support the use of NAET therapy in patients with allergies. Of several questions as to why this therapy appears to work may lie in the misdiagnosis of allergies or lack thereof. A significant concern is posed if a person has a true and severe allergy to a substance, and relies on this form of therapy to alleviate their reaction – they may be in danger of a reaction from exposure to an allergen causing anaphylactic shock (Teuber and Porch-Curren 2003).

In summary, the use of homeopathy or NAET therapy in the treatment of allergic diseases is not supported by a reputable body of literature. Thus, these treatment modalities are not recommended in the treatment or prevention of any allergic disease.

Conclusion

Despite the general lack of evidence of homeopathy to support its use as a safe and/or effective treatment for allergic (or any) diseases, its popularity remains high, and continues to grow. There are regulatory bodies in the United States (FDA) for homeopathy, but they do not evaluate these treatments for safety or efficacy.

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While in theory, homeopathic medications are extremely dilute, a brand which is labeled "homeopathic" may contain other substances that are not homeopathic, that may have an effect on a patient and/or the patient's conventional therapy.

Cross-References

- ▶ Allergen Immunotherapy, Overview
- ▶ Diagnostic Food Challenges
- ▶ Food Allergy, Overview
- ▶ Herbal Remedies
- ▶ Immunotherapy for Asthma

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Honeybee Allergy

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Synonyms

Apis mellifera

Introduction

As the primary pollinators in the world, bees have global significance. Honeybee (*Apis mellifera*) hives can be found in either the hives of beekeepers or in the case of feral (wild) honeybees in tree hollows, fallen logs, or buildings. Much has been made over the last few decades of Africanized honeybees which consist of hybrids from interbreeding of domestic honeybees and African honeybees from South America. Africanized honeybees are more aggressive species than domestic honeybees and may attack in swarms (Alaux et al. 2009). Though not pathognomonic for honeybees, upon stinging the honeybee typically leaves its barbed stinger and attached venom sac at the sting site. A sting was originally thought to deliver approximately 50 mcg of honeybee venom though subsequent evaluation has shown this to be variable.

Honeybee Entomology

The honeybee (*Apis mellifera*) includes the European honeybee (subspecies *A. mellifera ligustica*) and the African honeybee (subspecies *A. mellifera scutellata*). The African subspecies was introduced into the New World in the late 1950s. The Africanized honeybee, which has spread into several states including Texas, New Mexico, Arizona, Nevada, and California, is a hybrid of these two subspecies. Honeybees are

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eusocial defined by three traits: (1) care of young by cooperating members of the same colony; (2) reproductive division of labor, with sterile individuals working on behalf of fecund colony members; and (3) an overlap of two generations or more of adults within the same colony.

The Honeybee Hive

The feral honeybee hive may contain hundreds or thousands of honeybees (Bloch 2010) . With the exception of the Africanized honeybee, the honeybee is typically not aggressive when away from its hive and will only sting when provoked or stepped upon with bare feet. It is not uncommon to find yellow jackets within a honeybee hive as they are attracted to the honey within the hive.

Honeybee Venom

Honeybee allergens include nine venom proteins. The major allergens of honeybee venom include phospholipase A2 (Api m 1), hyaluronidase (Api m 2), and acid phosphatase (Api m 3). Melitin (Api m 4), dipeptidylpeptidase IV (Api m 5), Api m 6, CUB serine protease (Api m 7), carboxylesterase (Api m 8), and serine carboxypeptidase (Api m 9) are considered minor allergens (Georgieva et al. 2010) . Though it is not uncommon for venom from various flying Hymenoptera to share common antigenic components, honeybee venom infrequently cross-reacts with vespid (wasp, hornet, and yellow jacket) venom. The amount of venom delivered in a sting is variable and has been shown to range from 59 –141 mcg per sting. Honeybee venom is distinct from bumblebee venom though near identical to Africanized honeybee venom. Cross-reacting carbohydrate determinants (CCDs) in honeybee venom can cause cross-reactivity with *Vespula* venom which results in diagnostic testing in allergic patients positive to both (double positivity) honeybee and yellow jacket (Muller et al. 2009) . CCDs are contained in both plant and insect glycoprotein allergens and with hyaluronidase that are responsible for the cross-reactivity seen between honeybee and *Vespula* species. In addition to the characterization of honeybee venom proteins, sequencing of its genome has been completed which makes it a preferred model organism for species within the Hymenoptera family.

Evaluation of Allergy

All patients with a systemic reaction immediately after honeybee sting should be evaluated by an allergist. The rationale for this is that approximately 25–70 % of individuals with true venom allergy will experience a repeat reaction when stung again. Those with honeybee allergy are at a higher risk for repeat reaction than other flying Hymenoptera (Reference 17 in venom PP). It can sometimes be difficult for patients to correctly identify exactly which Hymenoptera stung them so geographic location and insect size, color, and shape may be helpful. Because of the difficulty with correct identification, allergists frequently will skin test patients to wasp, yellow jacket, yellow hornet, and/or white-faced hornet in addition to honeybee unless the sting occurred at the site of a honeybee keeper's hive. Local reactions at the sting site do not require formal evaluation by an allergist as these patients are not at a significantly increased risk for a more severe reaction with future stings to warrant immunotherapy.

In addition to gathering a thorough history to substantiate the systemic reaction related to suspected honeybee sting, skin testing is typically performed by allergists with standardized venom extracts. Commercial honeybee extract is available in a concentration of 100 mcg/mL and can be collected through either manual dissection of the venom sac or through "electric milking" which provides greater amounts of venom and is conducted when honeybees sting through a nylon net when they receive a high-frequency electric shock as they exit the hive. Skin prick testing is initially performed at a concentration of 1 mcg/mL followed by intradermal skin testing at an initial concentration of 0.001 or 0.01 mcg/mL and then followed by more concentrated tenfold

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dilutions to a max of 1 mcg/mL intradermal testing (Golden et al. 2011). A positive skin test is typically defined as a 5 mm wheal with surrounding erythema. Up to 50 % of patients will demonstrate double positivity to honeybee and vespids. This can be a result of true double sensitization if the patient has been stung to both honeybees and vespids or a result of cross-reactivity between the proteins or carbohydrates within the venoms. Protein microarrays in the form of component-resolved diagnosis (CRD) provide future promise as a basis for patient-tailored forms of venom immunotherapy with greater sensitivity and specificity than currently available with venom skin or serologic testing (de Graaf et al. 2009). CRD would allow assessment of specific IgE to the individual honeybee venom proteins (e.g., Api m 1–9). In addition, CRD requires small amounts of serum and may offer superior standardization and result interpretation (i.e., risk assessment for likelihood and severity of future sting reactions).

Honeybee Venom Immunotherapy

Those individuals with a positive history of a systemic reaction and positive skin testing demonstrating the presence of specific IgE to honeybee venom are recommended for immunotherapy with honeybee venom for a minimum of 3–5 years in most cases with extended courses in select patients. Extension beyond 3–5 years of therapy is a special consideration for honeybee as opposed to vespid allergy as honeybee allergic patients have a higher rate of relapse when off the honeybee venom therapy (Muller et al. 1992).

Honeybee venom immunotherapy is initiated with an initial injection of 0.1–1 mcg that is given with subsequent increasing doses delivered 1–2 times per week until a maintenance injection of 100 mcg/mL is reached and then spaced to once monthly injections. The 100 mcg/mL maintenance injection is delivered subcutaneously as a single-injection volume of 1 mL most frequently in the triceps arm region. The maintenance injection was originally thought to be equivalent to two stings (50 mcg/sting). Most recently, clinical practice is changing such that maintenance injections are spaced out to every 2–3 months with maintenance of efficacy and safety profiles seen with monthly injections (Goldberg and Reisman 1988; Kochuyt and Stevens 1994; Goldberg et al. 1994; Goldberg and Confino-Cohen 2001; Baenkler et al. 2005) .

Conclusion

The honeybee plays an integral role around the world and has a significant agricultural and allergic role with the environment and individuals which it interacts. As more is understood about the natural history for those with hypersensitivity to its venom, preventative and protective means will be more easily developed to provide assistance to those with a need. While similarities exist with other flying Hymenoptera, the honeybee has unique venom characteristics which set it apart and necessitate specific venom skin testing and therapy.

The opinions and assertions contained herein are the private views of the authors and are not to be construed as reflecting the views of the Department of the Air Force, the Department of Defense, or the United States Government.

Cross-References

- ▶ Biting Insects (Systemic and Local Reactions)
- ▶ Insect Allergy in Children
- ▶ Venom Content
- ▶ Vespid Allergy: Yellow Jackets, Hornets and Wasps

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Hypereosinophilic Syndromes

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Hypereosinophilic syndromes (HESs) is a different group of rare disorders defined by the presence of persistent peripheral blood eosinophilia (1,500 eosinophils/μl in blood), in the absence of any obvious reason of eosinophilia, such as parasitic or viral infections, allergic diseases, drug- or chemical-induced eosinophilia, hypoadrenalism, or nonhematological malignancies (Simon et al. 2010). HESs include platelet-derived growth factor receptor alpha (PDGFRA)–associated HES, lymphocytic variant HES (L-HES), familial hypereosinophilia, Churg-Strauss syndrome (CSS), organ-restricted eosinophilic disorders, and others (Simon et al. 2010). There are two categories for these difficult to diagnose disease: First, the cause might be due to increased production of cytokines-mediators that boost the differentiation and viability of eosinophils. These HES types are considered as "extrinsic eosinophilic disorders." The second major group of hypereosinophilic diseases is due to mutation-mediated clonal expansions of eosinophils and could be termed "intrinsic eosinophilic disorders" (Simon and Simon 2007). The most common cause of eosinophilia is the consequence of activated T cells producing high levels of IL-5 and/or other hematopoietins. The two different main subtypes of HESs are associated with dramatic differences in clinical presentation, prognosis, and responses to therapy. The availability of new targeted therapies, including tyrosine kinase inhibitors and humanized ▶ mAbs (Omalizumab), has only increased the importance of developing a better understanding of the etiologies and pathogenesis of HESs (Simon and Klion 2012).

Cross-References

- ▶ Eosinophil Activation
- ▶ Eosinophil, Definition and Morphology
- ▶ Eosinophil Historical Background
- ▶ Eosinophil Progenitors, Growth, and Differentiation and Death
- ▶ Eosinophil Receptor Expression
- ▶ Eosinophil Recruitment
- ▶ Eosinophils in Disease

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Hyper-IgE Syndrome

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Synonyms

Hyper-IgE Syndrome (HIES); Job´s Syndrome

Definition

Hyper-IgE syndrome is an inherited multisystem disease characterized by the classical triad of abscesses, pneumonia, and extremely elevated serum IgE.

Immunological and Non-Immunological Clinical Features

Job´s syndrome was first reported 1966 by Davis et al. on the basis of the case reports of two young girls with eczema, cold abscesses of the skin, and pneumonias (Davis et al. 1966). It was named Job´s syndrome in reference to the biblical Job whose body was affected with boils. Based on inheritance, an autosomal dominant (AD-HIES) and an autosomal recessive (AR-HIES) form of hyperimmunoglobulin E syndrome have been reported.

AD-HIES

The autosomal dominant form of hyper-IgE syndrome is a multisystem disorder. In addition to the classical triad (cold abscesses, pneumonia with pneumatocele, and extremely elevated IgE), it displays numerous immunological and non-immunological characteristics (Table 1). Among the immunological key features, an elevated and inappropriate inflammation is probably the most important feature. This is reflected by the coexistence of features like bronchiectasis and increased susceptibilities to opportunistic infections.

Dominant negative mutations in STAT3 account for the majority of cases of AD-HIES and are mainly missense mutations, with eventually occurring in frame deletions or exon skipping accounting for defects in the DNA-binding domain or the SH2 domain. Disease-causing mutations occur mainly sporadic (>90 %). Familial autosomal dominant inheritance is rare. From the two reported cases by Davis et al. in 1966, one individual was subjected to STAT3 gene analysis and a STAT3 mutation was confirmed. Two of her three male children with two men were affected from the disease (1 confirmed, 1 anticipated due to clinical symptoms) and one grandchild (Renner et al. 2007). In line with mouse data, Null alleles have not been detected and all mutations were found in only one allele, so far suggesting a dominant negative effect (Holland et al. 2007; Levy and Loomis 2007; Minegishi et al. 2007; Renner et al. 2007). STAT3 expression is not altered by the mutations, but STAT3 effector function is altered.

STAT3 is a key regulator of many cytokines and growth factors including γc cytokines (IL-2, IL-7, IL-9, IL-15, and IL-21), IL6/gp 130 cytokines (IL-6, IL-11, IL-27, IL-31, CNTF, CT1, oncostatin M, LIF), type 1 and 2 interferons (IFN-α, IFN-β, IFN-γ), IL10 family cytokines (IL-10, IL-19, IL-20, IL-22, IL-24, IL-26, IL-28, and IL-29), receptor tyrosine kinases (EGF, FGF, Flt3-L, GH, IGF1, M-CSF, PDGF), and IL-5, IL-12, IL-23, G-CSF, leptin, and PAF.

STAT3-dependent IL-6 and IL-23 signaling is impaired, expression of the Th17-related transcription factor RORγ is reduced, and Th17 cell responses are affected. AD-HIES patients are almost devoid of Th17 type responses known to be crucial for fungal repulsion or *Klebsiella* infections. This is on the one hand confirming the reported need of STAT3 for Th17 differentiation and is on the other hand in line with

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Hyper-IgE Syndrome, Table 1 Immunological and non-immunological characteristics of HIES

Immunological characteristics		
	AD HIES	DOCK8
Newborn rush	+++	+
Eczema	++++	++++
Recurrent S. aureus boils (often without cardinal features of inflammation like heat, erythema, tenderness)	+++	++
Recurrent pyogenic pneumonias (staph. aureus, strept. pneumoniae, haem. Influenzae)	++++	+++
Aberrant healing pneumatoceles and bronchiectasis Cutaneous viral infections	+++	+
Mucocutaneous candidiasis	+	++++
Peak serum IgE > 2,000 IU/ml	+++	++
Eosinophilia	+++	+++
Increased risk of malignancy	++++	++++
T-cell lymphopenia	+	+++
Diminished Th17 cell responses	–	+++
Extensive food and environmental allergies	+++	++
Eosinophilic lung disease and/or asthma	+	+++
Non-immunological characteristics	–	++++
Failure of primary teeth exfoliation	++++	–
Typical facial appearance	+++	–
(Facial asymmetry, deepset eyes, broad fleshy nose, prominent forehead and chin)		
Ridges of the oral mucosa on the palate and central depression of the tongue	++	–
Craniosynosthosis	++	–
Scoliosis	+++	–
Osteoporosis	++++	–
Hyperextensibility	+++	–
Minimal trauma a fractures	+++	–
Vascular abnormalities	+++	–
Central nervous abnormalities	+++	+
Chiari I malformation	+	–

data from patients with genetic defects in the IL17RA and IL17F gene (Puel et al. 2011) or patients with an AIRE defect (produce neutralizing anti-IL17A antibodies) who display insufficient IL-17-related responses and suffer from chronic mucocutaneous candidiasis. Moreover, Th17 cells are crucial amplifiers in neutrophil recruitment and tissue-related inflammation and are involved in IL-22 secretion and consequently β-defensin induction (BD2, BD3). IL-22 is downregulated in atopic dermatitis (AD) and is considered to be an important cytokine involved in the increased susceptibility to local *Staphylococcus aureus* infections in AD and also in HIES. Moreover, the deficiencies in IL-6 signaling may account for the relatively low C-reactive protein levels observed in AD-HIES patients during infections.

Peripheral blood derived mononuclear cells from HIES patients release increased levels of the pro-inflammatory mediators IFN-γ, IL-12, and TNF-α. IL-10 is a negative regulator that is crucial for negative feedback of macrophage activation and IL-10-producing T-regulatory cells. Defects in IL-10 signaling may contribute both to augmented inflammatory responses and increased IgE responses.

Antibody responses in HIES are considered to be within the normal range, but there are reports on defects in vaccination-related responses, responses to encapsulated bacteria, and also reduced numbers of circulating B-cells.

Conditional knockout models of STAT3 demonstrated poor wound healing, eosinophilia, cardiomyopathy, and lung and brain abnormalities. Myeloid-specific STAT3 deficient mice have elevated numbers of osteoclasts, leading to osteoporosis. Myocyte-specific STAT3-deficient mice develop heart failure and larger infarct areas after ischemic insult due to decreased endothelial and increased fibroblast proliferation (Scarabelli et al. 2008).

AR-HIES

More recently, DOCK8 mutations have turned out to be responsible for most forms of AR-HIES. The gene is highly expressed in immune cells and codes for members of the Rho-family GTPases, which have been linked to cell cycle, division, activation, differentiation, adhesion,

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and migration of cells. This is reflected in T-cell lymphopenia (both CD4+ and CD8+ T-cells) together with impaired in vitro expansion of T-cells. Non-immunologic symptoms reported for AD-HIES were mainly absent.

In 2006, one individual of the initially described 13 patients from six consanguineous families displayed a mutation in the tyrosine kinase 2 that is involved in the signaling pathway for IL-12, IL-5, and IFN-alpha. This patient did not display lymphopenia. So far only one Tyk2-deficient patient has been described lacking classical features like elevated IgE.

In 2009, Zhang et al. reported a case series of 11 patients with DOCK8 mutations that had elevated serum IgE levels, recurrent sino-pulmonary and cutaneous infections. Both male and female individuals with various ethnic backgrounds were affected. All included patients had atopic dermatitis, in two patients newborn rush was reported. The majority of the patients had allergies to inhalant antigens or food, eosinophilic esophagitis, anaphylaxis, asthma, or reactive airway disease. Other characteristic clinical features were recurrent upper and lower respiratory tract infections, recurrent otitis media, and recurrent sinusitis. Frequent cutaneous viral infections were reported (herpes virus, varicella zoster virus, human papilloma virus, molluscum contagiosum virus). Low IgM concentration and successive deficiency in secondary immunoglobulin production were described (Table 1).

A second series of DOCK8-deficient patients including one patient from the first report reproduced the main findings. However, lymphopenia was not observed in all patients with DOCK8 defects. Moreover, a general T-cell activation defect was observed that did not show a predominant CD8 affection (Engelhardt et al. 2009). In addition, neurologic complications like CNS bleedings or thrombosis, celiac artery vasculitis (Barlogis et al. 2011), and an increased susceptibility to malignancies were described. Other extra-immunological clinical manifestations of AD-HIES were not observed in patients with DOCK8 deficiency.

Therapy

No causal therapy of AD-HIES is known so far. Therapy is mainly supportive. The complexity of the disease requires a multidisciplinary approach. Prophylactic treatments with antibiotic and antifungal treatment to prevent pulmonary infections and aggressive antibiotic and antifungal treatment strategies based on active diagnostic methods may be indicated since clinical signs are often absent. This includes active surveillance diagnostic procedure like bronchoscopy to isolate causative pathogens at a very early time point. Antiseptic skin treatments are supportive. Bleach baths and swimming in chlorinated pools is effective via its *S. aureus* reducing effect. Immunosuppressive treatment of eczema is usually not indicated due to high rates of remission during antimicrobial treatment. Intravenous immunoglobulins may reduce the number of infections (Bilora et al. 2000). Case series of one patient with HIES and two patients with HIES and Kawasaki disease demonstrated a reduction of total IgE and eczema. Pneumatoceles are treated symptomatically. Resection requires careful decision making due to a high risk of complications. Two case reports of stem cell transplantation exist with limited success (one patient died at the 6 month of transplantation and the other patient displayed a relapse in IgE production and recurrence of infections).

Treatment options for AR-HIES (DOCK8 mutations) basically resemble those of AD-HIES. Eczema can be very difficult to treat with conventional local approaches and systemic immunosuppression via corticosteroids may be indicated but should be carefully considered since weaning may be difficult. This in turn may facilitate viral infections and development of opportunistic effects. Systemic immunoglobulin treatment is reported with varying success. The same holds true for interferon alpha treatment. Seven case reports of hematopoietic stem cell transplantation in patients with DOCK8 mutation exist. Five patients showed good response with resolution of skin manifestations and recurrent infections. Two patients died because of posttransplant complications

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(Bittner et al. 2010; McDonald et al. 2010; Barlogis et al. 2011; Gatz et al. 2011; Metin et al. 2012).

Cross-References

- ▶ IgE Testing
- ▶ Role of IgE in Disease

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Idiopathic Acute Eosinophilic Pneumonia

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Synonyms

Acute eosinophilic pneumonia (AEP); Idiopathic acute eosinophilic pneumonia (IAEP)

Definition

A histopathologic pattern of eosinophilic infiltration of the interstitium and alveolar spaces has been termed eosinophilic pneumonia (EP). Diseases with this underlying pattern have been further categorized based on primary (or idiopathic) or secondary (or known) etiologies. Secondary etiologies including drug toxicity and parasitic and fungal infections need to be excluded before a diagnosis of a primary EP can be made. Primary lung-limited EP conditions include idiopathic acute eosinophilic pneumonia (IAEP) and idiopathic chronic eosinophilic pneumonia (ICEP) (Cordier 2003). IAEP and ICEP differ with respect to clinical presentation, proposed diagnostic criteria, recommended therapies, and outcome.

Introduction

IAEP is a rare interstitial lung disease (ILD) with an underlying histopathologic pattern of EP. The disease is characterized clinically by the acute onset of respiratory symptoms often accompanied by respiratory failure requiring mechanical ventilation, imaging that reveals bilateral infiltrates, and an eosinophilic alveolitis on bronchoalveolar lavage (BAL). Because a peripheral blood eosinophilia is typically absent at the onset of disease, IAEP may be mistaken for acute lung injury or acute respiratory distress syndrome (Philit et al. 2002).

Historical Background

IAEP has only recently been recognized as a clinical entity. In 1989, Badesch and colleagues reported a case of idiopathic eosinophilic pneumonia identified on BAL and transbronchial biopsy, but the onset of symptoms was abrupt and the clinical features were not similar to those described in ICEP (Badesch et al. 1989). The patient, a 21-year-old male without a history of asthma or atopic disease, presented with acute dyspnea and hypoxemia. Imaging revealed diffuse bilateral, predominantly alveolar, infiltrates. In that same year, Allen and colleagues published a case series of four patients with underlying EP with similar clinical presentations and imaging findings to those reported by Badesch and

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colleagues (Allen et al. 1989). Additional case series have better defined the clinical, radiographic, and pathologic features of IAEP (Pope-Harman et al. 1996; Philit et al. 2002; Uchiyama et al. 2008; Hayakawa et al. 1994).

Epidemiology

IAEP is a rare condition; over the 20 years following the initial case reports, less than 100 cases had been reported in the literature (Janz et al. 2009). An epidemiologic study of military personnel deployed in or near Iraq reported an incidence of 9.1 cases per 100,000 person-years (Shorr et al. 2004).

Inhalational insults from tobacco smoke have been implicated as an etiology for disease. Of the cases of IAEP reported in the military personnel deployed in Iraq, all cases were smokers and most (78 %) had recently started smoking (Shorr et al. 2004). Additional data suggest that not only starting smoking but also restarting smoking after cessation and increasing the quantity of cigarettes smoked are associated with disease (Uchiyama et al. 2008). In smokers who were diagnosed with IAEP, rechallenge to tobacco smoke has been shown to result in symptoms of cough and dyspnea, a fall in PaO_2 and vital capacity, and worsening ground-glass opacities on imaging (Uchiyama et al. 2008).

Additional potential inhalational insults have been reported prior to the onset of disease and include cave exploring, plant repotting, wood pile moving, smoke house cleaning (Pope-Harman et al. 1996), gasoline tank cleaning, and exposure to tear gas (Philit et al. 2002). Exposures to both indoor dusts (from renovation work) (Philit et al. 2002) and outdoors dusts from extremely dusty conditions such as motorcross racing (Badesch et al. 1989) have also been reported. Of the military personnel in Iraq with IAEP, 95 % of cases had been exposed to dusts (Shorr et al. 2004). A New York City firefighter exposed to dusts from the World Trade Center developed IAEP; BAL fluid revealed a number of fibers including asbestos, chromium, and fibrous glass (Rom et al. 2002).

Pathogenesis

The pathogenesis of IAEP is unknown. Similar to ICEP, interleukin-5 (IL-5) is thought to be a central mediator of disease and is elevated in BAL fluid (Allen et al. 1996). IL-5 signals maturation, recruitment, and degranulation and promotes survival of eosinophils. How an exposure ultimately results in elevated IL-5 levels is yet to be determined, but there is likely some underlying predisposition given the rarity of disease (Janz et al. 2009).

Clinical Manifestations

IAEP occurs in young otherwise healthy persons. The mean age at onset varies between 20 and 30 years, and men appear to be affected more often than women. Symptoms are typically present for less than a week and include dyspnea, nonproductive cough, and fever. Some patients may experience chest pain, myalgias, and abdominal pain (Janz et al. 2009). Most often patients do not have a history of asthma. An atopic history may be present in some.

On physical examination, fever, tachycardia, and tachypnea are often identified. Chest auscultation may be normal or reveal crackles. Patients are typically hypoxemic, and respiratory failure requiring mechanical ventilation is not uncommon.

Diagnosis

Diagnostic Studies

At the onset of disease, the peripheral eosinophil count is usually normal but may become elevated over the course of the disease (Philit et al. 2002).

Radiographic imaging reveals diffuse bilateral infiltrates that may be either interstitial or alveolar in appearance with a non-segmental distribution. Kerley B lines and pleural effusions are also commonly seen (Pope-Harman et al. 1996). HRCT findings include bilateral areas of ground-glass attenuation, interlobular septal thickening, airspace consolidation, bronchovascular bundle

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thickening, and pleural effusions. The areas of ground-glass attenuation and airspace consolidation show a peripheral predominance in almost half of the cases (Daimon et al. 2008).

Similar to ICEP, BAL eosinophilia is a major diagnostic criterion in IAEP. In case series, the mean eosinophil percent on BAL has ranged from 36.9 % to 52.8 % (Janz et al. 2009). BAL should be performed in accordance with most recent practice guidelines in order to adequately sample the alveolar space (Meyer et al. 2012).

Histopathologic findings include the presence of acute and organizing diffuse alveolar damage with marked eosinophilic infiltration of the interstitium and alveolar spaces. Additional specific features reported in most patients include the presence of hyaline membranes and interstitial thickening due to edema, fibroblast proliferation, and inflammatory cells. Perivascular and intramural inflammation without necrosis may be seen (Tazelaar et al. 1997).

Diagnostic Criteria

Diagnostic criteria have been proposed and include the following: (1) the acute onset of respiratory symptoms (duration of <1 month), (2) bilateral infiltrates on chest radiograph, (3) hypoxemia (PaO_2 of ≤ 60 mmHg or oxygen saturation of <90 %), (4) eosinophilia of ≥ 25 % on BAL fluid or EP on lung biopsy, and (5) exclusion of other causes of EP including medications, illicit drugs, toxins, and infections (Philit et al. 2002).

Management

Similar to ICEP, patients have a dramatic response to corticosteroid therapy. Case series have reported that some patients will have spontaneous resolution of disease (Philit et al. 2002); however, given that fatal cases of IAEP have been reported (Shorr et al. 2004), most experts recommend treatment with corticosteroid therapy.

Typically, therapy is initiated in the form of intravenous methyprednisolone with daily doses ranging from 240 mg to 1 g. Transition to oral therapy (in the form of prednisone at doses between 40 mg/day and 60 mg/day) occurs after the patient is weaned from mechanical ventilation and can tolerate oral therapy (Janz et al. 2009). Treatment is tapered over 2–4 weeks, and unlike ICEP, the disease is rarely reported to recur.

Cross-References

- ▶ Eosinophil Activation
- ▶ Eosinophil Recruitment

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Idiopathic Chronic Eosinophilic Pneumonia

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Synonyms

Carrington's disease; Chronic eosinophilic pneumonia (CEP); Idiopathic chronic eosinophilic pneumonia (ICEP)

Definition

The term eosinophilic pneumonia (EP) is used to describe a histopathologic pattern of eosinophilic infiltration of the interstitium and alveolar spaces. Diseases with this underlying histopathologic pattern have been further categorized based on primary or secondary etiologies. Secondary EP may result from a variety of disease processes including drug toxicity, parasitic and fungal infections, and allergic bronchopulmonary aspergillosis/mycosis (ABPA/ABPM). Primary EP conditions are further categorized based on the presence of extrapulmonary manifestations (including Churg-Strauss syndrome and idiopathic hypereosinophilic syndrome) or based on lung-limited disease (including idiopathic chronic eosinophilic pneumonia (ICEP) and idiopathic acute eosinophilic pneumonia (IAEP)) (Table 1) (Cordier 2003). ICEP and IAEP differ with respect to clinical presentation, proposed diagnostic criteria, recommended therapies, and outcome.

Idiopathic Chronic Eosinophilic Pneumonia, Table 1 Primary and secondary disorders associated with eosinophilic pneumonia

Primary disorders associated with eosinophilic pneumonia	Secondary disorders associated with eosinophilic pneumonia
Lung predominant	Secondary chronic eosinophilic pneumonia
Idiopathic chronic eosinophilic pneumonia	Drug-induced pulmonary eosinophilia
Idiopathic acute eosinophilic pneumonia	Parasite-induced pulmonary eosinophilia
Systemic diseases	Fungal-induced pulmonary eosinophilia
Churg-Strauss syndrome	Allergic bronchopulmonary aspergillosis/mycosis (ABPA/ABPM)
Idiopathic hypereosinophilic syndrome	Bronchocentric granulomatosis

Introduction

ICEP is a rare interstitial lung disease (ILD) with an underlying histopathologic pattern of EP. The disease is characterized by the progressive onset of pulmonary symptoms including cough and dyspnea, and imaging that typically reveals peripheral pulmonary infiltrates. As a significant eosinophilia (either from the peripheral blood or from bronchoalveolar lavage (BAL)) is readily identified in the majority of patients, histopathology is rarely required. Given the unique features of ICEP, diagnostic criteria (see below) have been proposed (Marchand et al. 1998).

Historical Background

In 1969, Carrington and colleagues first defined the entity of idiopathic chronic eosinophilic pneumonia (ICEP) in a case series of nine patients (Carrington et al. 1969). These patients, who were all women, presented with an "unusual

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and distinctive syndrome" consisting of a life-threatening illness with breathlessness, fever, night sweats, and weight loss – symptoms initially concerning for either a chronic infection and/or malignancy. Radiographic imaging revealed dense, peripheral infiltrates that the authors described as the "photonegative" of pulmonary edema, and surgical lung pathology revealed eosinophilic infiltration of the interstitium and alveolar spaces. Interestingly, six of the nine patients described the development of asthma near or at the onset of the disease. Corticosteroid therapy rapidly improved both symptoms and imaging abnormalities. The outcome was considered to be good; however, the disease was reported to frequently recur after corticosteroid therapy was either tapered or discontinued.

Epidemiology

ICEP is a rare condition, and the prevalence and incidence are unknown. An ILD registry study in the United States found the prevalence of all-cause ILD was 80.9 cases per 100,000 population in men and 67.2 cases per 100,000 population in women; ICEP accounted for 1.2 % of the prevalent cases of ILD (Coultas et al. 1994). ICEP has been reported to account for as many as 2.5 % of prevalent cases of ILD in Europe (Thomeer et al. 2001).

Pathogenesis

The pathogenesis of ICEP is unknown. The lung injury that occurs in ICEP is thought to result in part from the release of toxic proteins from activated eosinophils (Janin et al. 1993). Increased production of IL-5, which signals maturation, recruitment, and degranulation, and promotes survival of eosinophils, is considered to be central to the disease pathogenesis. Increased concentrations of IL-5 have been identified in BAL fluid from diseased lung segments but not from uninvolved segments (Kita et al. 1996) and correlate with the percentage of eosinophils from BAL (Tateno et al. 2001).

In ICEP, increased numbers of activated CD4+ T-helper cells have been identified in BAL fluid (Mukae et al. 1995), and it is known that a subtype of these cells (Th2 cells) produce IL-5. However, the mechanisms that lead to the recruitment of these T-helper cells remain under investigation. Thymus- and activation-regulated chemokine (TARC-CCL17) and macrophage-derived chemokine (MDC-CCL22) – chemokines known to be involved with in the recruitment of Th2 cells – have been shown to be elevated in ICEP (Miyazaki et al. 2002; Manabe et al. 2005).

Clinical Manifestations

Since the initial description reported by Carrington and colleagues, additional case series have better defined the clinical features of ICEP (Jederlinic et al. 1988; Marchand et al. 1998). Women are more frequently affected with a sex ratio of 2:1. The mean age at onset is 45 years, but the disease has been reported to occur in both children and the elderly. While proposed diagnostic criteria (see below) suggest that symptoms need to be present for >2 weeks, most patients have symptoms for at least 4 months prior to diagnosis. Approximately 50 % of patients will report a history of asthma. The mean duration from the diagnosis of asthma to the onset of ICEP was 10.9 (± 10.9 years) in one series; however, the onset of asthma may occur at or after the onset of ICEP (Marchand et al. 1998). An atopic disease history may also be present. In comparison to IAEP, ICEP rarely occurs in smokers (<10 %).

Symptoms at the onset include breathlessness and cough in nearly all patients. While patients may be hypoxemic, overt respiratory failure requiring mechanical ventilation is rare. Pulmonary exam findings may reveal evidence of wheeze and/or crackles. Systemic symptoms include fevers, night sweats, malaise, and weight loss.

ICEP is considered a lung-limited disease process. Rarely, additional single organ involvement has been reported including acute pericarditis, arthralgias, mononeuritis multiplex,

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diarrhea, hepatitis, urticaria, and purpura. However, any extrathoracic manifestation should raise the possibility of alternative diagnosis of either Churg-Strauss syndrome or idiopathic hypereosinophilic syndrome; Churg-Strauss syndrome has been reported to occur after an initial diagnosis of ICEP (Hueto-Perez-de-Heredia et al. 1994).

Secondary Chronic Eosinophilic Pneumonia

The development of chronic eosinophilic pneumonia has been associated with both rheumatoid arthritis and radiation therapy. Given the association with either a concurrent disease process or pulmonary insult, the term secondary chronic eosinophilic pneumonia (SCEP) has been recommended by some (Olson et al. 2006). Clinical features, radiographic abnormalities, and histopathologic findings of SCEP are similar to ICEP. In association with rheumatoid arthritis, SCEP has been reported to occur in both established diseases (Payne and Connellan 1980) and prior to the initial diagnosis (Olson et al. 2006). Cottin and colleagues reported the occurrence of SCEP after radiation therapy for breast cancer in a case series of five female patients (Cottin et al. 2004). The mean age was 68 years, and all patients had a history of asthma and/or atopic disease. Radiation-associated SCEP occurred at a median time of 3.5 months (range 1–10 months) after radiation therapy. Management strategies similar to ICEP have been employed in SCEP, and relapse has been reported.

Diagnosis

Diagnostic Studies

Laboratory analysis typically reveals evidence of a peripheral absolute eosinophil count of >1,000 cells/μL (in ~ 80 % of patients). IgE levels are elevated in 50 % of patients, but typically not to the degree reported in ABPA. Markers of inflammation (including ESR and CRP) are elevated in the majority of patients (Marchand et al. 1998). Pulmonary function tests may reveal obstruction or restriction or may be normal. The diffusion is reduced in up to 50 % of cases.

Chest radiograph abnormalities typically include bilateral, peripheral alveolar infiltrates. The disease is localized to either the upper lungs in 50 % or to the upper and lower lungs in 40 % of cases; rarely is it a basilar predominant process (Marchand et al. 1998). The characteristic pattern of dense peripheral consolidation – or the photonegative of pulmonary edema reported by Carrington – is present in only 25 % of cases (Jederlinic et al. 1988). Infiltrates may be migratory in a quarter of cases and pleural effusions are rare. Computed tomography is more sensitive for the detection of parenchymal abnormalities and usually reveals bilateral, ground-glass, and consolidative abnormalities in a cranial-caudal distribution similar to that of chest radiographs. Interlobular thickening, centrilobular nodules, and pleural effusions may be seen (Arakawa et al. 2001).

BAL eosinophilia is a major diagnostic criterion in ICEP; in one series, over 80 % of patients were found to have an eosinophil percentage of > 40 % on differential cell count from BAL fluid (Marchand et al. 1998). Elevated neutrophil and lymphocyte percentages are observed, but these percentages should be lower than the eosinophil percentage for an accurate diagnosis. BAL must be performed in accordance with recent guidelines to adequately sample the alveolar spaces (Meyer et al. 2012). Degranulated eosinophils (with a multinucleated nucleus) may resemble neutrophils – particularly on Wright's stain (Cordier 2003).

If required, pathology from surgical lung biopsy reveals eosinophilic infiltration of both the alveolar spaces and the interstitium. Additional inflammatory cells including lymphocytes, macrophages, and neutrophils may be present. Foci of organizing pneumonia are not infrequently reported. Intra-alveolar macrophages and neutrophils may contain eosinophilic granules and Charcot-Leyden crystals. Eosinophilic inflammation may extend into vessels walls, but a granulomatous or necrotizing vasculitis is not present and suggests an alternative diagnosis (Marchand et al. 1998).

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Diagnostic Criteria

Diagnostic criteria have been proposed and include the following: (1) peripheral predominant pulmonary infiltrates (consolidation with air bronchograms and/or ground glass) on chest imaging, (2) eosinophil percentage of $\geq$40 % on bronchoalveolar lavage differential cell count and/or peripheral blood eosinophilia of $>$1,000/cells, (3) respiratory symptom duration of $>$2 weeks, and (4) exclusion of other causes of EP (including exposure to drugs and infections).

Bronchoalveolar lavage is typically employed in the diagnosis of ICEP, not only to confirm the diagnosis with evidence of alveolar eosinophilia but may also be used to rule out infection. Typical clinical and radiographic features with peripheral blood eosinophilia strongly suggest the diagnosis of ICEP. Surgical lung biopsy is rarely required, but may be of necessary if diagnostic ambiguity remains (Cottin and Cordier 2012).

Management

The response corticosteroid therapy is dramatic with symptomatic and radiographic improvement occurring within days (Marchand et al. 1998). Thus, recommendations from expert opinion indicate that corticosteroid therapy should be initiated, typically in the form of prednisone, at a dose of 0.5 mg/kg/day to 1 mg/kg/day (Marchand and Cordier 2006). Thereafter, corticosteroid therapy is generally tapered over several weeks to a maintenance dose and continued for usually at least 6 months (Bhatt and Allen 2012). The maintenance dose required is variable; Marchand and colleagues found that in patients who relapsed during weaning, the mean dose of corticosteroid therapy at relapse was 10.7 $\pm$ 9.4 mg/day (Marchand et al. 1998).

Recommendations to treat for at least 6 months is based on a case series that found that almost all patients treated for less than 6 months relapsed, while those without relapse at long-term follow-up were nearly all treated for longer than 6 months (Marchand et al. 1998). Relapse is common and long-term follow-up has found that the majority of patients will require prolonged corticosteroid therapy for either disease control and/or refractory asthma. Some data have suggested that inhaled corticosteroid therapy may reduce the maintenance dose required (Naughton et al. 1993) and the risk of relapse (Marchand et al. 2004), but this is controversial.

Cross-References

- ▶ Eosinophil Activation
- ▶ Eosinophil Recruitment

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Idiopathic Pulmonary Fibrosis

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Synonyms

Cryptogenic fibrosing alveolitis; IPF

Definition

Idiopathic pulmonary fibrosis (IPF) is a progressive fibrotic interstitial pneumonia of unknown cause that is limited to the lungs, seen primarily in the elderly, and has no approved pharmaceutical therapies in the USA outside of lung transplant.

Historical Background

The first conclusive necropsy finding of IPF was published in 1898, describing large amounts of fibrous tissue and cystic spaces in the lung and coining the term "cirrhosis cystica pulmonum" (Rindfleisch 1898). Hamman and Rich published the first observations of an acute diffuse interstitial fibrosis in 1933, and the entity now known as IPF was defined over the following 20 years (Homolka 1987). Recent international evidence-based guidelines on the diagnosis and management of IPF have been published (Raghu et al. 2011).

Epidemiology/Prevalence

The estimated prevalence of IPF is 14–43 per 100,000 in the United States (Raghu et al. 2006). An estimated 0.5–3.7 % of these are familial cases with described mutations in surfactant protein C, surfactant protein A, telomerase reverse transcriptase, and telomerase RNA component (Lawson et al. 2011). Mortality for IPF is 64 deaths per million in men and 58 deaths per million in women. The attributable mortality of IPF is increasing; rates have increased 28 % in men and 41 % in women from 1992 to 2003 with most patients dying from the lung disease itself (Olson et al. 2007). A number of environmental associations have been identified including smoking, metal dusts, wood dusts, and exposure to livestock (Taskar and Coultas 2006).

Pathogenesis

The pathogenesis of IPF is unknown. It involves recurring damage to the epithelium of the lung in

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the setting of abnormal wound healing. There is dysregulated epithelial-mesenchymal crosstalk that leads to the accumulation of myofibroblasts. This occurs in the setting of a pro-angiogenic and Th2-oriented profile with multiple cytokines and growth factors mediating this fibrotic response (Datta et al. 2011).

Clinical Manifestations

IPF is a disease of aging and most patients present in their 6th or 7th decade. It is seen more commonly in men and smokers. Patients complain of dry cough and/or the insidious onset of shortness of breath. Examination often reveals bibasilar inspiratory crackles on pulmonary exam and the presence of clubbing with signs of right heart failure in severe cases.

Diagnosis (HRCT, Path)

An accurate diagnosis of IPF requires a multidisciplinary approach involving a clinician, radiologist, and pathologist, and the likelihood of disease increases with agreement between the clinical characteristics, radiographs, and histopathology (when available). The diagnosis of IPF requires the exclusion of other known causes of interstitial lung disease and either the presence of a usual interstitial pneumonia (UIP) pattern on high-resolution computed tomography (HRCT) (see below) or a combination of HRCT findings and characteristic findings on histopathology (Raghu et al. 2011). In its classic form, the HRCT reveals basilar and peripheral predominant reticulation with associated honeycombing and an absence of significant ground glass changes. With these classic changes, a radiologist can make an accurate diagnosis (one that correlates with lung biopsy) in over 90 % of cases (Hunninghake et al. 2001). Histopathology reveals a patchy subpleural and paraseptal pattern of involvement with areas of scarring alternating with uninvolved lung parenchyma. The involved lung shows dense collagen with scattered foci of proliferating fibroblasts (called fibroblastic foci) (Katzenstein and Myers 1998). Pulmonary function tests show restriction (with low lung volumes) and reductions in diffusion capacity that correlate with the severity of the disease. Hypoxemia is a universal finding at later stages of the disease.

Management

In the early years of IPF management, anti-inflammatory and immunomodulatory agents such as corticosteroids, cyclophosphamide, and azathioprine were utilized. Due to a lack of convincing evidence as to their efficacy, current guidelines recommend against their use (Raghu et al. 2011). Starting in 2004, there have been a number of prospective placebo-controlled trials looking at novel agents including interferon-gamma, etanercept, sildenafil, imatinib, bosentan, ambrisentan, and warfarin. None of these trials demonstrated significant effects on the primary outcome (including time to disease progression, 6-min walk test, and changes in physiology over time) (Cerri et al. 2012). More recently, the PANTHER trial was conducted to look a therapy with prednisone, azathioprine, and N-acetylcysteine, a combination found in an earlier study to have a significant effect on the decline in physiological variables. The PANTHER study was stopped at interim analysis due to an increase in mortality and hospitalizations in the treatment group (Raghu et al. 2012). Finally, pirfenidone, a synthetic nonpeptide with antifibrotic and anti-inflammatory properties approved for use in Europe, Japan, and India, has shown discordant results in two randomized trials, and a third trial (the ASCEND trial) is ongoing (Noble et al. 2011). There are many actively enrolling clinical trials in IPF and details can be found at www.clinicaltrials.gov. Transplant remains the only viable option for patients with progressive disease, and patients should be referred to a transplant center early in the course of their treatment (George et al. 2011).

Acute exacerbations, defined as a clinical worsening in symptoms and CT scan over 30 days without a cause (such as infection, pulmonary embolism, or heart failure), are common in IPF (Kim 2012). Recommended therapy for

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exacerbations in the current IPF guidelines includes high-dose corticosteroids (though this is based on antidotal reports of efficacy) (Raghu et al. 2011).

With the current lack of effective pharmacologic therapy for IPF (outside of pirfenidone in Europe, India, and Japan), nonpharmacological therapy as well as the management of comorbidities is critical. Maintenance of normoxia during rest, activity, and sleep helps improve symptoms and quality of life. Pulmonary rehabilitation improves functional capacity and fatigue in patients with IPF and should be utilized (Swigris et al. 2011). Finally, clinicians should have a low threshold to evaluate for and treat concomitant conditions such as pulmonary hypertension, gastroesophageal reflux, and obstructive sleep apnea.

As the clinical course of IPF is often complicated by respiratory failure, end-of-life issues should be discussed early on in their treatment course with attention given to the poor outcomes of patients with IPF on mechanical ventilation (Stern et al. 2001).

Prognosis

The prognosis of IPF is poor – patients have a mean survival of 3–5 years. Though the typical clinical course is that of gradual increase in shortness of breath accompanied by worsening physiology and progression of fibrosis on HRCT, there are several possible natural histories for IPF patients. A subset of patients will remain stable over many years. Others have a rapid decline either early in the course of their illness or after a prolonged period of stability (Martinez et al. 2005). Acute worsenings are common, either from secondary complications such as pneumonia or exacerbations of the underlying fibrotic lung disease. Factors affecting the progression of IPF and predictors of these clinical phenotypes are currently unknown.

Conclusions

Idiopathic pulmonary fibrosis is a progressive fibrotic interstitial pneumonia of unknown cause. It is more common in male smokers, and patients often present in their 1960s and 1970s with progressive shortness of breath and cough. CT scans typically show a pattern of peripheral and basilar fibrosis with honeycombing, and histopathology reveals pleural-based heterogeneous fibrosis with clusters of fibroblasts termed fibroblastic foci. There are no approved therapies in the United States, and clinical trials are ongoing. Though heterogeneity exists in the clinical course, it is typically one of progression with a mean survival less than 5 years. Transplant is a viable treatment option in patients with IPF.

Cross-References

- ▶ Testing: DLCO
- ▶ Testing: High-Resolution Chest Computed Tomography Scan

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IgE Isotype Switching

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Synonyms

IgE class switch recombination

Definition

Gene rearrangement within the immunoglobulin heavy chain locus of a B lymphocyte, resulting in expression of the IgE immunoglobulin heavy chain

Immunoglobulin Heavy Chain

To understand the process of immunoglobulin isotype switching (also referred to as class switch recombination (CSR)), it is important to understand the structure of the immunoglobulin (Ig) heavy (H) chain locus. Each Ig molecule consists of two heavy (IgH) and two light chains, both of which contain variable (V) and constant (C) regions. The genes encoding the heavy chains of human immunoglobulins are located on chromosome 14. The region of the heavy chain that determines antigen specificity is made up by the variable (V_H), diversity (D), and joining (J_H) exons that are randomly combined during early B cell development to form a $V_H(D)J_H$ cassette. The $V_H(D)J_H$ is located upstream of the C exons. The C region of the IgH chain determines the isotype of the Ig. Each C_H gene has its own promoter, an intervening (I) exon, and a switch (S) region directly upstream of the coding exons (Casellas et al. 1998; Honjo 1983). In mature naïve B lymphocytes, the $V_H(D)J_H$ cassette is linked to the constant region of the μ chain (Cμ) (Schatz and Ji 2011). Consequently, mature naïve B cells express surface IgM and, as a result of alternative splicing, IgD as their B cell receptor (BCR) (Illustrated in Fig. 1).

Basic Mechanism of Class Switch Recombination

Upon activation, naïve B cells can undergo CSR, a process in which the B cell changes the isotype of the produced immunoglobulin while its antigen specificity is retained. There are nine human IgH chain isotypes: IgM, IgD, IgG1, IgG2, IgG3, IgG4, IgA1, IgA2, and IgE and eight murine Ig isotypes: IgM, IgD, IgG1,

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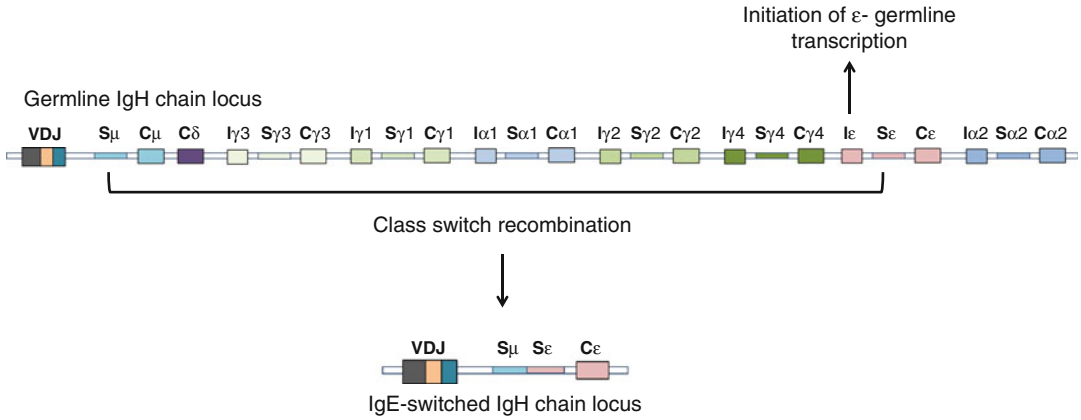
Initiation of ε- germline transcription
Germline IgH chain locus
VDJ Sμ Cμ Cδ Iγ3 Sγ3 Cγ3 Iγ1 Sγ1 Cγ1 Iα1 Sα1 Cα1 Iγ2 Sγ2 Cγ2 Iγ4 Sγ4 Cγ4 Iε Sε Cε Iα2 Sα2 Cα2
Class switch recombination
VDJ Sμ Sε Cε
IgE-switched IgH chain locus

IgE Isotype Switching, Fig. 1 Organization of the human immunoglobulin heavy chain locus in mature naive B cells and class switch recombination to IgE. Mature naive B cells carry the germline IgH chain locus. These cells have their rearranged VH(D)JH domain located directly upstream of the Cμ domain and as a result they express IgM and IgD as surface receptors. CSR to IgE is requires ε-germline transcription and finally results in the generation of double strand DNA breaks at Sε followed by ligation of the Sμ to Sε

IgG2a, IgG2b, IgG3, IgA, and IgE (Honjo 1983). Essentially CSR is the process in which double strand breaks are generated at two different S regions within the IgH chain locus followed by the deletion of the intervening DNA and ligation of the remaining S regions. The S regions are located upstream of the gene segments encoding the various IgH chains. The generation of double strand (ds) DNA breaks at selected S regions requires the activity of several enzymes that include activation-induced deaminase (AID), uracil DNA glycosylase (UNG), and apyrimidinic/apurinic endonuclease (APE) (Honjo et al. 2002). The expression of ε-germline transcripts precedes CSR to IgE and is required for IgE synthesis. The proposed mechanism by which germline expression facilitates CSR is the "accessibility model." This implies that germline transcription (induced by cytokines) leads to opening of the chromatin structure of the S region, making it accessible to AID. AID converts cytosines to uracils in such a transcriptionally active S region (Chaudhuri et al. 2003; Nambu et al. 2003; Petersen-Mahrt et al. 2002). These uracils can be excised by the DNA base excision repair enzyme UNG, leading to the generation of abasic sites that can be processed by APE1, leading to the formation of nicks and ultimately result in dsDNA breaks (Schrader et al. 2005). The dsDNA breaks are repaired by the nonhomologous end-joining repair system, resulting in the ligation of a downstream C_H region (Cε in the case of IgE CSR) next to the VDJ gene segments (Casellas et al. 1998) (Fig. 1). The ends of the excised DNA can be joined resulting in the formation of an extrachromosomal circular DNA (also referred to as excision circle). These excision circles can be detected using PCR and are indicative of a recent CRS event.

Distinct Features of IgE Isotype Switching

There are no indications that CSR to IgE differs mechanistically from CSR to other Ig isotypes. Transcription initiation at the Iε promoter is required for CSR to IgE and subsequent IgE production. Therefore, the determining factor for CSR to IgE is active ε-germline transcription which makes the Sε region accessible for AID. The key factors that determine the Ig isotype that will result from CSR are the ones that regulate

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S region germline transcription. These factors are primarily cytokines and in the case of CSR to IgE, IL-4 and IL-13 are the primary inducers of ε-germline transcription. A more detailed description of the events that specifically drive the induction of IgE will be discussed later on in "Induction of IgE synthesis; cellular interactions and molecular events."

However, IgE is by far the least abundant immunoglobulin isotype. Circulating IgE levels in normal healthy individuals typically comprise less than 0.05 % of the total Ig concentration. This brings up the question: What distinguishes induction of IgE from that of other isotypes such as IgG? There are indications that, at least in mice, the generation of high-affinity IgE antibodies results from sequential CSR. This implies that naïve B cells initially switch to IgG1 and undergo affinity maturation in germinal centers after which some cells may switch from IgG1 to IgE. Furthermore, it has been demonstrated that IgE-switched B cells are mostly absent from the germinal centers, indicating that CSR to IgE does not readily take place in germinal centers. Low affinity IgE antibodies on the other hand typically result from direct CSR to IgE occurring outside of germinal centers (Xiong et al. 2012) Furthermore, BCL6-deficient mice which lack germinal centers have normal IgE levels, indicating that germinal center formation is not required for IgE induction. Direct evidence for the requirement of sequential CSR through IgG for the generation of high-affinity IgE antibodies is not available for humans, but there are some indications, as reviewed in (Aalberse and Platts-Mills 2004). Human IgG4, much like murine IgG1, is induced in a Th2-dependent manner. Based on the observation that seasonal increases in specific IgE antibody titers in patients with pollinosis are much slower and smaller than IgG responses, it has been proposed that the IgE memory compartment is likely small and/or poorly established. An explanation for this observation may be that the high-affinity IgE-switched B cells which either derive from germinal center IgG-switched precursors or from naïve B cells that directly switched to IgE do not give rise to memory cells but either differentiate to plasma cells or undergo apoptosis. Increased susceptibility to apoptosis of IgE-switched B cells has indeed been observed in high-density in vitro cultures.

Cross-References

▶ Induction of IgE Synthesis: Cellular Interactions and Molecular Events

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IgE Receptor

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Synonyms

High affinity IgE receptor/FCeRI; Low affinity IgE receptor/FcεRIIb/CD23

Definition

Cell surface receptor that specifically binds IgE.

IgE Receptors

There are two Fc receptors that specifically bind IgE through interaction with its Fc region: the high-affinity IgE receptor FCεRI and the low-affinity IgE receptor FCεRII, also known as CD23. Furthermore a protein called galectin-3 which is primarily secreted from macrophages can bind IgE as well as FcεRI. Galectin 3 is a 30 kDa galactoside-binding lectin that can form pentamers in complex with oligosaccharides which are present on IgE and FcεRI. As a result, galectin-3 can activate mast cells and basophils by cross-linking FcεRI directly or indirectly through receptor-bound IgE molecules (Gould and Sutton 2008).

High-Affinity IgE Receptor

FcεRI is expressed on mast cells, basophils, epidermal Langerhans' cells, dendritic cells (DC), monocytes, and, under certain conditions, intestinal epithelial cells. The human FcεRI can be expressed as a tetrameric or a trimeric receptor whereas murine FcεRI is only expressed as a tetramer. The tetrameric receptor is expressed by mast cells and basophils and is composed of three different membrane-bound chains: the α, β, and γ chains (Blank et al. 1989). The α-chain belongs to the immunoglobulin (Ig) superfamily, and it contains an extracellular IgE-binding domain, a transmembrane domain, and a cytoplasmic tail. Expression of the human (but not murine) FcεRIα chain can be upregulated by IL-4. The β-chain has four transmembrane domains that function as signal amplifiers, while the two γ-chains that form a homodimer consisting of a transmembrane domain and a cytoplasmic tail are required for initiation of receptor-mediated signaling. The trimeric form of FcεRI lacks the β chain and is expressed on antigen-presenting cells (monocytes, Langerhans cells, and DCs) and eosinophils (Kraft and Kinet 2007).

FcεRI expression enables cells to stably interact with IgE molecules through high-affinity binding of the Fc portion of these antibodies to the α-chain of FcεRI, forcing the antigen-specific regions of the IgE molecules to stick out and function as sentinels for their specific antigens. When multivalent allergens bind to cell surface–bound IgE molecules, FcεRI is cross-linked and, depending on the cell type, cells either release a distinct set of preformed pro-inflammatory mediators (degranulation) or they internalize the captured allergens for subsequent antigen presentation. The early events following antigen-mediated cross-linking of IgE bound to FcεRI are activation of proto-oncogene tyrosine-protein kinase Src (SRC)-family kinases followed by tyrosine phosphorylation of cytoplasmic FcεRIβ- and γ-associated immunoreceptor tyrosine-based activation motifs (ITAMs). These phosphorylated ITAMs provide docking sites for SH2 domains of tyrosine-protein kinase Lyn (LYN), ZAP70, and spleen tyrosine kinase (SYK) which will activate the linker for activation of T cells (LAT) protein which is central to many of the downstream signaling cascades that are required for the release of pro-inflammatory mediators (reviewed in more detail in Gilfillan and Tkaczyk (2006); Kraft and Kinet (2007)). Degranulation upon allergen binding occurs in sensitized mast cells and basophils, leading to the release of preformed mediators such as histamine and heparin, and the rapid synthesis

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of leukotrienes, prostaglandins, cytokines, and chemokines. This reaction is referred to as the immediate hypersensitivity reaction. Cross-linking of IgE bound to FcεRI receptors on antigen-presenting cells (APC) such as Langerhans cells and DC can result in internalization and processing of allergens. This leads to presentation of allergen fragments on MHC class II molecules together with co-stimulatory molecules, enabling activation of allergen-specific CD4+ T cells. Compared to normal APC, sensitized DC or Langerhans cells demonstrate an increased affinity for specific allergens which enhances the efficiency of allergen internalization. The allergen concentration required for activation of allergen-specific T cells is significantly reduced when APC carry allergen-specific IgE molecules on FcεRI (Maurer et al. 1995).

Low-Affinity IgE Receptor

The low-affinity IgE receptor FcεRII/CD23 is the only known Fc receptor that is a type II surface glycoprotein. All other Fc receptors are type I proteins. Type I membrane proteins have a cytoplasmic N terminus and an extracellular C terminus, whereas type II membrane proteins have an inverted orientation (Kinet 1989). The extracellular portion of CD23 contains a C-type lectin domain which facilitates IgE binding and an α-helical coiled-coil stalk which drives the formation of trimers in the cell membrane (Beavil et al. 1992). CD23 is encoded by an 11-exon gene located at chromosome 19p13.3. There are two isoforms of CD23 (CD23a and CD23b) that result from differential transcription initiation and alternative splicing (Acharya et al. 2010). CD23a is constitutively expressed on B cells and can be efficiently internalized whereas CD23b expression can be induced on B cells, macrophages, and keratinocytes by IL-4 and/or LPS and does not internalize efficiently. Because of the relatively low binding affinity, stable binding of IgE to this receptor occurs mostly when multiple IgE molecules are clustered in complexes (Dalloul et al. 1992; Karagiannis et al. 2001; Yokota et al. 1992). CD23 can be cleaved from the cell surface by ADAM10 and Der p1 (a house dust mite derived protease and a major allergen) yielding soluble (s)CD23 proteins of different sizes (Schulz et al. 1995; Weskamp et al. 2006).

Besides IgE, a number of other ligands have been described for CD23. These include CD21 and αMβ2-integrin, αXβ2-integrin, αVβ3-integrin, and αVβ5-integrin (Gould and Sutton 2008). sCD23 can have a pro-inflammatory effect as it binds to the αMβ2-integrin and αXβ2-integrin on monocytes which respond with nitric oxide production, cyclic adenosine monophosphate synthesis, and the production of pro-inflammatory cytokines like TNF, IL-1, and IL-6 (Rezzonico et al. 2001). CD23 and CD21 have been proposed to coordinately regulate IgE production. The binding surfaces on CD23 for IgE and CD21 are spatially separated, which means that CD21 and IgE can bind simultaneously to CD23 (Hibbert et al. 2005). CD23 can interact with CD21 in soluble as well as membrane-bound form. Interaction of membrane-bound CD21 and CD23 can aid in cell-cell adhesion of B cells through homotypic adhesion (Bjorck et al. 1993). CD23 has been proposed to regulate IgE production both positively and negatively. sCD23 may positively regulate IgE production through simultaneously binding CD21 and membrane IgE on IgE-switched memory B cells. This will culminate in the formation of an extensive signaling platform that might promote the survival and differentiation of IgE-switched B cells. Negative regulation of IgE production can occur by co-ligation of membrane-bound CD23 and IgE by allergen-IgE complexes (Gould and Sutton 2008).

IgE-Facilitated Antigen Presentation Through the Low-Affinity IgE Receptor

CD23 has been demonstrated to increase the antigen-presenting capacity of B cells through a mechanism referred to as IgE-facilitated antigen presentation (IgE-FAP). B cells are able to internalize, process allergens, and present

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allergenic peptide fragments on MHC class II molecules. This results in the activation of allergen-specific CD4+ T cells. B cells expressing CD23 on their surface membrane can bind immune complexes (IC) consisting of IgE antibodies and allergens in a B cell receptor–independent manner. This results in the cross-linking of CD23 molecules and subsequent internalization of IC by means of receptor-mediated endocytosis. This mechanism of antigen capture is much more efficient than the uptake and presentation of allergens via pinocytosis and results in the activation of CD4+ T cells at a 100–1,000-fold lower allergen concentration (van Neerven et al. 2006). Therefore, IgE-FAP could be a major contributor to the induction of CD4+ T cell responses after exposure to low allergen doses. The relevance of this mechanism has been demonstrated for several respiratory allergies such as birch pollen or house dust mite allergy reviewed in van Neerven et al. (2006). The first study showing the mechanism of IgE-FAP was published in 1989. This study demonstrated that 2,4,6-trinitrophenol TNP-IgE complexes could bind to B cells via CD23, resulting in internalization and activation of TNP-specific T cells (Kehry and Yamashita 1989). It has been shown that IgE-allergen complexes can induce up to 10-fold stronger T cell responses in vivo than the allergen on its own (Getahun et al. 2005). The first human studies comprised incubation of purified Der p II with sera from atopic patients containing Der p II–specific IgE. Subsequently, EBV-transformed B cells were incubated with these IC and used as APC in a lymphocyte proliferation assay. This resulted in strong proliferation of Der p II–specific T cells at a 1,000-fold lower allergen concentration than required for T cell activation by uncomplexed Der p II. These enhanced antigen-presenting properties are abolished by treatment with anti-CD23 or anti-IgE, stressing that antigen focusing is largely dependent on CD23-IgE interaction. No other APC than B cells show significant surface expression of CD23a on their surface membrane. Interestingly, IgE-FAP circumvents the need for an antigen-specific B cell in order to efficiently capture antigens. Therefore, it has been proposed that this mechanism could be an important contributor to epitope spreading (Gould and Sutton 2008).

Cross-References

▶ Activating and Inhibitory Receptors on Mast Cells

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IgE Testing

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Synonyms

Immunoglobulin E testing

Definition

Immunoglobulin E is an immunoglobulin subtype that is considered to play a key role in repulsion of parasites. In addition, it plays a key role in the pathogenesis of allergy. In conjunction with clinical history, measurement of allergen-specific IgE represents a central tool to diagnose allergy.

History

Although clinical cases of pollen induced hay fever were reported at the beginning of the nineteenth century, it took more than 100 years to find out that a serum-related factor was responsible. Especially the famous experiment by Prausnitz and Küstner (1921) in which passive intradermal transfer of serum from Küstner who was allergic to fish led to allergic local reactions in Prausnitz (Prausnitz and Küstner 1921; Prausnitz 1955) represents a crucial step. However, due to the extremely low concentration of the mediating factor, it took another 25 years until IgE was discovered. In 1960s, two groups worked on the responsible factor to elicit histamine release. The group of Ishizaka who worked on the reagin that mediated histamine release reported in 1966 and 1967 to have an antiserum to precipitate the "reagin" and thereby decrease activity. Since it became apparent that it did not belong to any of the so far known immunoglobulins, it was termed γE-globulin (Ishizaka et al. 1964, 1966). However, despite further efforts, Ishizakas group did not succeed in purifying the respective γE-globulin. In a parallel experiment, Johansson and Bennich found an atypical myeloma protein that had striking similarities with the reagin (Johansson 1967; Johansson and Bennich 1967; Stanworth et al. 1967). Moreover, a counterpart in sera of healthy individuals and, to a much higher degree, in the sera of allergic asthmatics was described. This counterpart was termed IgND. Based on this finding a sandwich-based immunoassay, the radioallergosorbant test (RAST) was developed from SGO Johansson in collaboration with L Wide (Wide et al. 1967).

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Further evidence for a crucial role of IgND in allergy was provided by dose-dependent inhibition of Prausnitz and Küstner reaction by isolated IgND (Stanworth et al. 1967). In 1967, reagents were exchanged by the groups of Ishizaka and Johansson and in 1968, the new immunoglobulin was called IgE (Ishizaka et al. 1966).

The RAST technology revolutionized allergy diagnosis. It was based on a very simple principle. A matrix bound allergen extract is exposed to the sera and after washout, a secondary labeling step with a radiolabeled anti-IgE antibody allows relative estimation of the specific IgE in sera of humans. Initially, there was considerable doubt about the relevance of RAST technology in comparison to the skin prick test. Moreover, the definition of cut-off values separating normal from elevated IgE levels and standardization was a constant issue of debate. Throughout the last 15 years, several modifications occurred. Three of these adaptations have to be mentioned. First, the substitution of radiolabeled antibodies by enzyme-tagged monoclonal detection antibodies. Second, the development of solid phases with higher allergen-binding capacities. Third, the introduction of fluid phase allergen, which is bound to solid phase after complexation with fluid phase IgE. Initially, mainly allergen extract was used and subsequently, purified allergens became available. Thereafter, recombinant allergens were generated and component resolved diagnosis became reality. Nowadays, epitope-specific approaches are under way.

Quantification of IgE

Several methods were used to measure IgE in serum: immunodiffusion in agar, radial immunodiffusion in agarose with detection of precipitins via radiolabeled antiserum, competitive displacement radioimmunoassay (RIA), two-sided immunoradiometric assays (IRMA), two-sided enzyme immunoassay (EIA), and kinetic nephelometry. Both immunodiffusion methods are lacking sensitivity to detect IgE in sera.

Several important considerations have to be taken. Specific IgE antibodies to be quantified co-occur with antibodies of the same specificity from the same but also from different isotypes. An excess of major and minor allergens is crucial. It makes it on the one hand less likely that other isotypes have an inhibitory effect and forms the basis to quantify all bound antibodies in an affinity independent manner. Another important point is the fact that anti-IgE antibodies need to be specific for the Fc region instead of affinity purified polyclonal antibodies raised against IgE.

To quantify IgE, the inclusion of a standard curve is necessary. Standard reference materials of total and specific IgE should be traceable to the WHO International Reference Preparation of Human IgE (2nd International Reference Preparation, 1980; 75/502) to achieve a certain degree of comparability.

Total IgE Measurement

Serum total IgE concentrations increase steadily with age and reach levels of adults at the age of 5–7 years. Normal values in a population-based sample of children within the age of 1–6 years of white children from Germany have been published recently (Kulig et al. 1999). Boys tended to have higher levels. However, there were no significant differences within the atopic group. Although total IgE in general is a poor marker to predict allergic disease, total IgE levels beyond two standard deviations correlate with allergic disease in childhood. However, total IgE levels within the normal range do not exclude allergic disease. In childhood, asthma in general is tightly linked to atopy and consequently total IgE is elevated very often. Nevertheless, the clinical value is very limited. In asthmatic adults, only 50 % of patients with exogen allergic asthma and 5 % of patients with non-atopic asthma have elevated total IgE levels. Total IgE measurement in patients receiving anti-IgE treatment (omalizumab) is not possible due to interference with the assay. Indications to measure total IgE based on the AWMF guideline on in vitro allergy diagnosis 2009 are listed in Table 1.

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IgE Testing, Table 1 Indications for total IgE measurement (From Renz et al. 2009. With permission)

In connection with specific IgE measurement • Supporting evidence for atopic predisposition • To provide supporting interpretation in the interpretation of antigen-specific IgE
Diagnostic tool to link the disease to an atopic phenotype • Urticaria, Quincke´s edema, eosinophilic gastroenteritis, exanthemas of unknown origin, suspicion of drug induced hypersensitivity
Cases with comparable differential diagnosis • Eosinophilic infiltrates, exogen allergic alveolitis, Wegener´s disease, Churg-Strauss syndrome, Allergic bronchopulmonary aspergillosis
Diagnosis and therapy control • Parasitic diseases, in particular in if eosinophilia with no evidence for parasitic infestation
Acquired and inherited immunodeficiency • T-cell defects or hyper-IgE syndrome

Specific IgE Measurement

Specific IgE is defined as IgE that specifically binds an allergen and defines allergic sensitization. However, the presence of specific IgE does not necessarily imply clinical symptoms to the allergen sensitized to. Clinical relevance needs to be assured via patient history recording clear-cut exposure-related clinical symptoms and in case of doubt and justified from an ethical point of view via challenge procedures (e.g., double-blind placebo-controlled food challenge in case of food allergy).

Specificity of allergen-specific IgE measurement in first line depends on the quality of the allergen extract or purified allergen on the one hand (folding; exposure of IgE binding sides, stability) but also on the nature of the allergen itself (minor vs. major allergen, cross-reactivity due to amino acid sequence or degree of glycosylation).

Numerous tests to detect specific IgE are on the market, the principles however relate to the basic mechanism of solid phase or fluidic phase bound allergens that are quantified by secondary radio, enzyme or immunofluorescence-labeled anti-IgE antibodies (Fig. 1). The amount of specific IgE is determined by the intensity of the respective signal. WHO International Reference Preparation of Human IgE is used as calibration material. Due to the multiple confounding factors that impact specific IgE quantification, absolute values cannot be directly compared. In general, but not always, the ImmunoCap system from Fisher Scientific is used as internal control standard.

Cross-Reactive Carbohydrate Determinants

N-glycosylation of proteins is widely distributed in plant and insect proteins. The carbohydrate parts represent a group of pan-epitopes. IgE to these cross-reactive carbohydrate determinants (CCD) has been reported to be present in up to 30 % of sera from allergic patients. This leads to false-positive results since the clinical relevance of such CCD specific IgE is considered to be minimal. Glycosylation motives prototypically have an α 1,3 fucose core and a xylose end branch. Potential strategies to screen for IgE CCD include the testing for binding to polyvalent glycoproteins like horseradish peroxidase or bromelain.

Molecular Diagnosis

Advances in the understanding of allergen biochemistry and the generation of recombinant allergens resulted in the characterization of major and minor allergens from different protein families that contributed to a better understanding of allergic diseases. The aim of these approaches is to separate individuals sensitized without clinical reactivity from patients with clinically relevant allergy. Moreover, it harbors the possibility to shape immunotherapy based on individual sensitization patterns. Molecular diagnosis is available as conventional ImmunoCap but also as a microarray-based detection system from different companies which allow to screen for more than hundred allergens with a serum volume of less than 100 µl. Consequently, simple IgE measurement is replaced by an IgE profile which allows having an overview of potential cross-reactive allergens, CCD patterns, and across allergen families.

Recombinant and purified allergens are spotted in defined amounts and all used allergens are represented in comparable amounts (Fig. 2).

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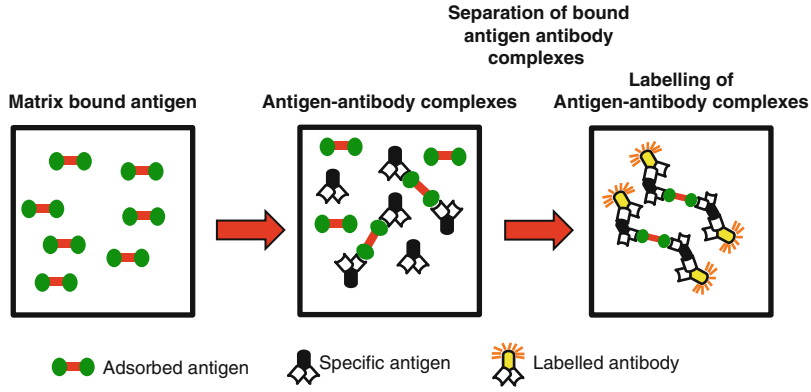
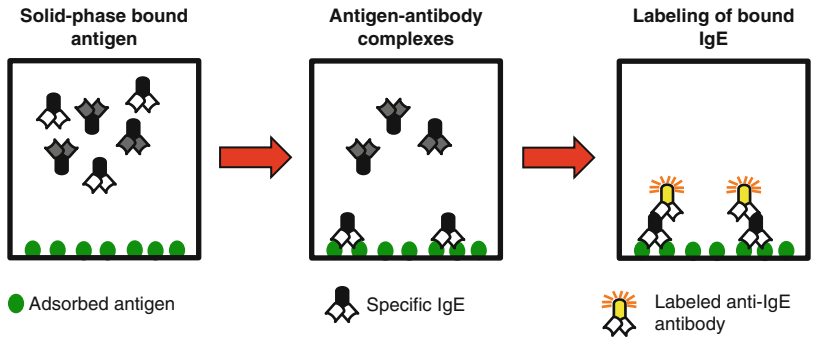


IgE Testing, Fig. 1 Indirect two-sided immune-radiometric assays (IRMA, RAST)



IgE Testing, Fig. 2 Surface immobilized allergen-based detection system (microarray)

Extracts that have been used before the era of component resolved diagnosis differed considerable with regard to allergen composition. One of the advantages of microarray technologies is also the low amount of antigen needed (ng). On the contrary, quantification of specific IgE is not as precise.

Cross-References

- ▶ Genetic Regulation of IgE
- ▶ Role of IgE in Disease

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IgE-Secreting Plasma Cells

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Synonyms

Effector B cells; Immunoglobulin-producing B cells; Plasma B cells; Plasmacytes; Terminally differentiated B cell

Definition

Plasma cells are terminally differentiated B cells that secrete large quantities of antibody. In the case of IgE-producing plasma cells, these antibody-producing cells produce large amounts of the immunoglobulin isotype, IgE, as opposed to those that secrete any one of the other isotypes (e.g., IgM, IgG1, IgG2, IgG2a, IgG2b, IgG3, IgG4, IgA, IgA1, and IgA2). Like all white blood cells, plasma cells are ultimately of bone marrow origin where they begin development into B cells. Once leaving the bone marrow, B cells migrate to secondary lymph tissue (e.g., lymph nodes) where terminal differentiation into plasma cells is possible (Achatz-Straussberger et al. 2009).

Historical Background

A history leading to the identification of plasma cells as antibody-producing cells has been described in detail elsewhere (Potter 2007). In brief, the famous histologist Ramon y Cajal is credited with first describing plasma cells in 1890 after seeing them in syphilitic condylomas. He initially suggested they might be derived from embryonic tissue since they were unlike any other leukocyte. Marschalko was the first to suggest that plasma cells originated from emigrated blood lymphocytes, having seen them in many kinds of tissue. Nonetheless, many investigators continued to believe these cells originated from a connective tissue cell, the "reticular cell." This was despite the observations by James Wright in 1906, describing the prevalence of plasma cells in the bone marrow of subjects with multiple myeloma. In 1948, Astrid Fagraeus reported in her eloquent thesis work evidence that convinced most workers in the field that plasma cells were, indeed, the source of antibodies, noting a high concentration of these cells in the red pulp of the spleen. Naturally, the notion of IgE-producing plasma cells would not come for another 20 years later when, in 1966, IgE was identified as a new immunoglobulin isotype responsible for the reaginic activity in the serum of allergic and asthmatic patients (Ishizaka et al. 1966; Johansson 1967). Soon after the discovery of IgE, clinical examples of IgE myeloma provided solid evidence for plasma cells producing monoclonal forms of this immunoglobulin isotype.

Although IgE is the least common of the immunoglobulin antibody isotypes, essentially all individuals have detectable levels in serum that range between 25 and 100 ng/mL (10–40 kIU/L) in nonatopic adult subjects (Poulsen and Hummelshoj 2007). Moreover, essentially all of the IgE in nonatopic subjects, as well as 70–80 % of that in atopic subjects, lacks specificity for any known antigen. Thus, there is seemingly an evolutionary advantage for maintaining the production of IgE, despite its association with the pathogenesis of allergic disease. This persistence likely stems from this class of antibody playing a critical role in the defense against multicellular parasites, such as helminthes and ticks – a physiologic function long hypothesized for IgE.

Development of IgE Plasma Cells

The development of plasma cells in general involves a complex sequence of differentiation events (Poulsen and Hummelshoj 2007).

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The precursors of plasma cells, B cells, begin development in the fetal liver and, in adult life, in the bone marrow. While in the bone marrow, the process of differentiation is completed with the successful rearrangement and expression of the B cell receptor (BCR), which, in this instance, is the expression of IgM subclass of immunoglobulin. However, before leaving the bone marrow, B cells also gain the co-expression of IgD. These IgM-IgD double positive B cells then enter circulation in the blood and lymph in order to target secondary lymph tissue, such as lymph nodes and spleen. Only after encountering antigen via the IgM/BCR do B cells begin the process of differentiating into plasma cells. Moreover, complex interaction with other cell types is needed to complete this transformation and to determine the exact isotype of antibody produced by the terminally differentiated plasma cell.

Several critical immunological events are needed before the development of IgE-producing plasma cells is possible (de Vries et al. 1991). Foremost, there is an absolute requirement for IL-4 and/or IL-13 to initiate the isotype switching of IgM-positive B cells to those expressing IgE (Gauchat et al. 1990). T-helper type 2 cells (Th2) are classically thought to provide the initial source of IL-4/IL-13, but exactly how naïve T cells take on a Th2 phenotype is in of itself a poorly understood process. Recent studies point to interactions with DCs primed in a particular manner (Liu 2009). For example, in vitro studies show that myeloid DCs preexposed to the epithelial-derived cytokine, thymic stromal lymphopoietin (TSLP), cause these cells to mature into antigen-presenting cells expressing OX40L. The subsequent interaction between OX40L on DCs with OX40 on naïve T cells during antigen presentation causes the T cells to develop into so-called inflammatory Th2 cells producing IL-4 among other Th2 cytokines, including IL-13 and IL-5. Naturally, this IL-4 can then play a critical role in causing isotype switching from IgM to IgE in B cells. However, it should also be noted that more recent evidence has challenged this concept by arguing that basophils may very well be an important source of IL-4 and IL-13 for initiating Th2 responses and for the induction of IgE synthesis (Schroeder 2011). In this scenario, in vivo studies done in mice show that basophils can be activated by serine proteases (which are common to many allergens as well as helminthes) to produce IL-4, thus directly impacting Th2 development and subsequent IgE synthesis by B cells (Sokol et al. 2008).

The activation of B cells toward the development of plasma cells initiates with the binding of antigen to the BCR, which coincides with increases in major histocompatibility complex (MHC) class II and co-stimulatory molecules (e.g., CD80/86) that are important for interactions with T cells. Only B cells that bind antigen with high enough affinity continue to secrete antibody and differentiate into plasma cells. In contrast, B cells that bind antigen with low affinity end up undergoing apoptosis. Assuming that one and/or both of the IL-4/IL-13-producing events mentioned above occur simultaneously, then these cytokines have the capacity to act on B cells to initiate intracellular signals that activate STAT6. This transcription factor is then critical for the induction of μ and ε germline transcription resulting in IgE class switch recombination (CSR) (Poulsen and Hummelshoj 2007). Another important signal required for IgE class switch recombination (CSR) is that mediated between CD40L on T cells with CD40 on B cells. This interaction results in the activation of NFκB and is important for maximal IgE germline production. In vitro studies show that activated basophils can also express CD40L, thus providing both of the necessary signals (IL-4/IL-13 being the other) to induce IgE isotype switching in B cells (Gauchat et al. 1993). Of course, CSR is the process that exchanges the constant region of the heavy chain with a set of downstream constant-region genes. With regard to IgE isotype switching, this process involves the excision of genomic DNA spanning from the Sμ sequences to the Sε sequence. Ligation of variable, diverse, and joining (VDJ) sequences to the constant (C) ε locus then results in an intact ε heavy chain gene and the production of intact IgE antibodies.

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Upon activation and following CSR to IgE, some B cells take on memory cell capacity and can become rapidly activated at a later time if antigen is encountered (Duchosal 1997). Indeed, low levels of antigen can seemingly persist on follicular DC for years and can continually activate B cells to maintain memory cell populations and/or activate B cells to become full-fledged plasma cells. These processes are thought to contribute to the ability of an individual to maintain low levels of specific Ig (including IgE) for many years, even when avoidance of antigen/allergen is well documented.

Development into plasma cells is then accompanied by several maturational events that associate with these cells being end stage in development. For example, plasma cells no longer retain the capacity to divide or to respond to antigen and typically downregulate MHC class II expression along with classic B cell markers (e.g., CD19, CD20, CD22, CD44, and CD45) (Calame 2001). Fully developed plasma cells are larger than B cells, appearing as cells with an acentric nucleus and a large parachute-shaped cytoplasm with large amounts of endoplasmic reticulum and a pronounced Golgi. Plasma cells may survive for only a few weeks or become long lived if located to specific niches such as the bone marrow where they can survive for months providing high-affinity antibody.

As noted above, IgE titers are the lowest of all the major immunoglobulin classes, indicating that IgE production is tightly regulated (Achatz-Straussberger et al. 2009). Foremost, the serum half-life of IgE (in humans) is on the order of 1–5 days. For comparison, the half-lives of IgG1, IgG2, and IgG4 are on the order of 21–24 days. In addition, whereas IL-4 and IL-13 are essential for IgE synthesis, there are several cytokines that regulate this immunoglobulin by inhibiting its synthesis, including IL-12, TGF-β, IFN-γ, and IFN-α. Most recently, IL-21, a type I cytokine sharing homology with IL-2, IL-4, IL-7, IL-9, and IL-15, is reported to enhance IgE production by human B cells co-stimulated in vitro with anti-CD40 antibody and IL-4. However, this cytokine was shown to have suppressive activity toward IgE production in an in vivo mouse model. In addition to inducing IgE isotype switching, IL-21 is also reported to influence the production of IgG and IgA and thus has proliferative as well as apoptotic activity on B cells depending on their stage of development. Ongoing work is being conducted to fully discern the role of this cytokine in IgE synthesis (Konforte et al. 2009).

IgE Plasma Cells in Disease

Although there is preponderance for increased specific IgE in most kinds of allergic disease, these conditions are not necessarily known for marked increases in IgE-producing plasma cells. In contrast, there are at least two known conditions that are characterized by a gross overproduction of IgE and thus marked increases in the numbers of IgE plasma cells. Foremost, extremely rare cases of multiple myeloma have been described whereby the antibody isotype produced is IgE, rather than IgG as in most instances. As noted above, multiple myeloma is a cancer of plasma cells (generally in bone marrow) and is the second most common hematological malignancy, constituting 1 % of all cancers. Interestingly, it has been proposed that plasma cell leukemia is a more common feature in IgE myeloma, compared to those associated with the production of other immunoglobulin classes. In particular, one case report noted circulating IgE-producing plasma cells exceeding 30 % of the white blood cell count (West et al. 1983).

Hyperimmunoglobulin E syndrome (HIES) is another condition associated with very high IgE serum levels, often exceeding 2,000 IU/mL (Sowerwine et al. 2012). This primary immunodeficiency syndrome (also known as Job's syndrome) is recently linked to dominant negative mutations in the DNA-binding region of the STAT3 transcription factor. HIES is characterized by recurrent "cold" staphylococcal infections, eczema-like skin lesions, and lung infections with pneumatocele-like lesions – hence, the reference to Job, who in the Bible was cursed by Satan to walk the earth with sores

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covering his body. At least one study reports being able to detect IgE-producing plasma cells exceeding 5 % of the $CD138^+$ cells circulating in blood, which was on the order of 100-fold greater than the frequency detected in nonatopic subjects (Horst et al. 2002). Whether mutations in STAT3 are linked to the overproduction of IgE remains poorly understood, although this seems highly probable in light of this transcription factor having a role in the signaling mediated by cytokines negatively regulating IgE synthesis, including IL-10, IL-21, and IL-17.

Cross-References

- Analytes and BIOMARKERS: IgE
- Diagnostic Components: T Helper Cell Cytokines (IL-4, IL-5, IL-9, IL-10, IL-13, IL-17)
- Genetic Regulation of IgE
- Hyper-IgE Syndrome
- Induction of IgE Synthesis: Cellular Interactions and Molecular Events
- Role of IgE in Disease

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Immunomodulator Therapy of Asthma

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Synonyms

Bronchial asthma

Definition

The working definition of asthma taken from the National Asthma Education and Prevention Program Expert Panel Report 3: "Asthma is a chronic inflammatory disorder of the airways in which many cells and cellular elements play a role: in particular, mast cells, eosinophils, neutrophils (especially in sudden onset, fatal exacerbations, occupational asthma, and patients who smoke), T lymphocytes, macrophages, and epithelial cells. In susceptible

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individuals, this inflammation causes recurrent episodes of coughing (particularly at night or early in the morning), wheezing, breathlessness, and chest tightness. These episodes are usually associated with widespread but variable airflow obstruction that is often reversible either spontaneously or with treatment" (Busse et al. 2007).

Immunomodulator Therapy

The standard therapy for the treatment of bronchial asthma is the use of inhaled corticosteroids in association with a short acting bronchodilator, as the severity of asthma increases the addition of a long-acting bronchodilator with or without a leukotriene antagonist is a step up. The next step up is the use of an anticholinergic, then systemic corticosteroid. More directed immunomodulator therapies have emerged. The only one available clinically is omalizumab, a monoclonal humanized antibody that binds the allergy immunoglobulin IgE. Other monoclonal antibody therapies are in the experimental realm.

Omalizumab

Omalizumab is a monoclonal IgG kappa antibody which binds to the IgE domain that binds to activate the Fc IgE receptor. This results in the downregulation of the IgE Fc receptors and further reduction of the activation of the IgE target cells. It was found to be effective as a steroid-sparing agent in oral steroid-dependent asthmatics (Lafeuille et al. 2012; Sweeney et al. 2012; Vennera et al. 2012).

Experimental Therapies

Mepolizumab

Mepolizumab is a humanized monoclonal antibody that binds to the eosinophil growth factor interleukin-5 (IL-5). Initial therapeutic trials adding mepolizumab to the therapeutic regimen of asthmatics failed to show any benefit (Flood-Page et al. 2007). However, once a subgroup of severe steroid-dependent asthmatics who have sputum eosinophilia was targeted, mepolizumab was found to be highly efficacious. In this subgroup, mepolizumab reduced the dose of systemic steroids needed therapeutically and showed significant improvement in their quality of life (Haldar et al. 2009; Nair et al. 2009).

Reslizumab

Reslizumab is a humanized IgG4 Kappa monoclonal antibody which also binds IL-5 (Castro et al. 2011). This confers on it the ability to remove IL-5 and reduce eosinophilia. Given the role eosinophils play in lung inflammation in asthma, it is also being experimentally studied for the treatment of asthma. Reslizumab is made by a company other than mepolizumab. It was found to be effective in reducing the systemic corticosteroid dose and improving the quality of life in patients with eosinophilic-severe-steroid-dependent asthma (Castro et al. 2011; Molfino et al. 2012).

Benralizumab

Benralizumab is a humanized monoclonal antibody that binds the alpha subunit of the IL-5 receptor. It is undergoing studies in patients with bronchial asthma (Busse et al. 2010). The hypothesis on its mechanism of action (Ghazi et al. 2012; Molfino et al. 2012) suggests that it interferes with the function of IL-5 by antibody-mediated cellular cytotoxicity.

Silencing Small Messenger RNA

TPI ASM8

TPI ASM8 is an antisense RNA directed against the common beta chain of the receptors for IL-3, IL-5, GM-CSF, and CCR3 (receptor for eotaxin an eosinophil chemotactic factor). It effectively inhibits the formation of those receptors and, henceforth, the effect of the mediators. Those mediators play an important role on the generation of eosinophils and their migration to the lung in asthma. In an inhaled form, it was found to inhibit allergen-induced asthma exacerbation (Gauvreau et al. 2008; Gauvreau et al. 2011). This finding opens a whole new field of inflammatory modulation without the application of

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monoclonal antibodies. Furthermore, TPI ASM8 is delivered directly to the lung by inhalation and not systemically.

Cross-References

- Allergen Avoidance: Avoidance Strategies for Skin Allergies
- Allergen Avoidance: Cockroach and Rodent Avoidance
- Allergen Avoidance: Dietary Management of Food Allergy
- Allergen Avoidance: Dust Mite Avoidance
- Allergen Avoidance: Fungi and Mold Avoidance
- Allergen Avoidance: Furry Animal Avoidance
- Allergen Avoidance: Pollen Avoidance - Tree, Grass, and Weed
- Allergen Immunotherapy, Overview
- Analytes and Biomarkers: Environmental Allergen Assessment
- Analytes and Biomarkers: Nitric Oxide (NO) and Asthma
- Asthma Variants: Allergic Asthma
- Asthma Variants: Cough-Variant Asthma
- Bronchial Challenges
- Cotinine
- Diagnostic Terms: Atopy
- Diseases in DDx of Asthma: Alpha 1 AT Deficiency
- Diseases in DDx of Asthma: Bronchopulmonary Dysplasia
- Diseases in DDx of Asthma: COPD
- Diseases in DDx of Asthma: Croup
- Diseases in DDx of Asthma: Differential Diagnosis of Asthma
- Diseases in DDx of Asthma: Vocal Cord Dysfunction
- Eosinophils in Disease
- Exercise Challenge
- Exhaled Nitric Oxide
- Immunotherapy for Asthma
- Mannitol Challenge
- Methacholine Challenge
- Methods (In Vivo) Provocation Tests (Nasal Challenge, Bronchial Challenge, Food Challenge)
- Role of IgE in Disease
- Role of Mast Cells in Diseases
- Safety of Immunotherapy
- Specific IgE
- Testing: DLCO
- Testing: High-Resolution Chest Computed Tomography Scan
- Testing: Sputum Eosinophil Count
- Topical Corticosteroids

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Immunomodulator Therapy of Chronic Urticaria

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Synonyms

Chronic hives; Hives; Urticaria; Wheals

Definition

Chronic urticaria (CU) is a heterogeneous group of dermatologic disorders characterized by the presence of wheals (areas of swelling of the epidermis, hives, or urticarial lesions) that are erythematous and markedly pruritic for a period of more than 3 days a week lasting 6 consecutive weeks or longer (Hollander et al. 2011). There are multiple etiologies for CU but most patients have idiopathic urticaria.

Immunomodulator Therapy

The initial line of therapy for patients presenting with urticarial is the use of non-sedating antihistamines even at four fold the recommended dose if the patient does not respond to standard therapeutic doses with the addition of leukotriene antagonists (Fonacier et al. 2010). These therapeutic interventions often fail leaving the options for therapeutic intervention not FDA approved for the therapy of CU. Alternative therapies include the use of colchicine, dapsone, hydroxychloroquine, sulfasalazine, methotrexate, cyclosporine, and mycophenolate mofetil. Newer experimental therapies include intravenous immunoglobulin and omalizumab (Fonacier et al. 2010).

Colchicine

Colchicine is an alkaloid which is FDA approved for the treatment of gout, gout prophylaxis, and prophylaxis in familial Mediterranean fever. Its mechanism of action in those and other disorders is not known. It has some success in treatment of CU recalcitrant to first-line therapies and can be successfully used as a steroid-sparing agent. In one recent retrospective study, a review of 35 patients with CU treated with colchicine, 56 % of the patients had a subjective complete or partial remission (Pho et al. 2011). The most common side effect of colchicine is diarrhea, but a few patients can experience nausea and vomiting. The serious side effect is myelosuppression. Concomitant use of a CYPA4 inhibitor, such as most protease inhibitors, can results in fatal renal and hepatotoxicity. Rhabdomyolysis and neuromuscular toxicity can occur at higher doses or in the presence of renal or hepatic dysfunction. Clinical monitoring of patients is of critical importance. This should be accompanied by monitoring for myelosuppression with a complete blood count and differential, liver enzymes, and serum creatinine.

Dapsone

Dapsone is a systemic antibacterial agent indicated for the therapy of leprosy in combination with other agents. It is also used in the treatment of acne vulgaris and dermatitis herpetiformis. Its mechanism of action in dermatitis herpetiformis as well as CU is unknown. Patients should be screened for the level of glucose-6-phosphate-dehydrogenase (G6PD) before they receive dapsone. G6PD is needed to metabolize dapsone and prevent the development of hemolytic anemia. In the absence or reduced activity of G6PD, the development of hemolytic anemia could be fatal. There are multiple case reports showing dapsone to be an effective steroid-sparing agent,

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and a good therapeutic option for CU (Fonacier et al. 2010; Noda et al. 2012).

Hydroxychloroquine

Hydroxychloroquine is an antimalarial drug that is efficacious in some autoimmune disorders. There are a few reports in the literature showing that it provides and immunomodulatory for some patients with recalcitrant idiopathic urticarial (Reeves et al. 2004). Like other immunomodulator medications, it requires monitoring for toxicity. It should not be used with other hepatotoxic drugs or in patients with liver disease. Annual evaluation for the development of retinopathy is important as well. It can cause serious side effects such as torsades de pointes, myelosuppression, fulminant hepatic failure, drug-induced myopathy or neuromyopathy, and hearing loss. Patients receiving it should be under close clinical and laboratory monitoring.

Sulfasalazine

Sulfasalazine is an immunomodulatory agent effective in the treatment of ulcerative colitis and rheumatoid arthritis. It has been reported as effective in the treatment of some patients with recalcitrant CU (McGirt et al. 2006). Its main side effects include itching, abdominal pain, and other gastrointestinal symptoms. The concerning side effects include a small likelihood for the development of Stevens Johnson's Syndrome, hepatotoxicity, myoneural disorder, systemic lupus, kidney disease, and pulmonary fibrosis. Patients receiving it should be closely monitored both clinically and by laboratory studies.

Methotrexate

Methotrexate is a reversible inhibitor of dihydrofolate reductase. By this inhibition, it interferes with DNA synthesis, replication, and repair. Its exact mechanism of action in different disorders remains to be elucidated. It is FDA approved for the treatment of rheumatoid arthritis, severe psoriasis, and a number of hematologic and solid organ malignancies. Its side effects include myelosuppression, gastrointestinal bleeding, stomatitis, hepatotoxicity, renal toxicity, and neurotoxicity. If used the patients have to be monitored closely, both clinically and by laboratory studies. It is available in both oral and intravenous forms. It has been described as successful steroid-sparing agent in the treatment of recalcitrant CU (Perez et al. 2010; Sagi et al. 2011). If used concomitant use of folic acid supplementation is recommended. It is teratogenic and, therefore, should not be used during pregnancy.

Calcineurin inhibitors

Cyclosporine

Cyclosporine is an anti-inflammatory, immunosuppressive calcineurin inhibitor. Its exact mechanism of action in different disorders is unknown. It is, however, felt to act by reducing the levels of IL-2 and, henceforth, reducing T-cell activation. It is mainly used for patients who undergo transplantation. Cyclosporine has been reported to successfully control recalcitrant CU and work as a steroid-sparing agent (Di Leo et al. 2011; Hollander et al. 2011). Its main side effect is renal toxicity and the development of hypertension. It is therefore important to monitor the blood pressure of patients receiving it. Laboratory monitoring should include serum creatinine, potassium, magnesium, liver enzymes, complete blood count and differential as well as a cyclosporine trough level.

Mycophenolate Mofetil

Mycophenolate mofetil is another calcineurin inhibitor most commonly used for prevention of transplant rejection. Its molecular mechanism of action is different from that of cyclosporine. It is mostly eliminated through the kidney, dose adjustments are needed in renal failure. Like cyclosporine, it can cause hypertension, hypokalemia, and hypomagnesemia. It is a myelosuppressive agent and can be neurotoxic or cause gastrointestinal bleeding. Patients receiving it should be monitored closely. Blood pressure checks and signs of infection are the main clinical symptoms and signs that need to be followed. Laboratory studies should include all the elements that it can affect as listed above. There have been two reports in the literature showing its benefit as a steroid-sparing agent in

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patients with severe CU who failed other therapeutic modalities (Shahar et al. 2006; Zimmerman et al. 2012).

Experimental Therapies

Intravenous Immunoglobulin (IVIG)

Intravenous immunoglobulin is FDA approved for the use in patients with primary immunodeficiencies, infection prophylaxis in patients with chronic B-cell lymphocytic leukemia, hepatitis A prophylaxis, idiopathic immune thrombocytopenic purpura, chronic inflammatory demyelinating polyradiculopathy, Kawasaki disease, measles prophylaxis, post exposure prophylaxis rubella in pregnancy, measles prophylaxis when varicella zoster immune globulin is not available and motor neuropathy with multiple conduction blocks. It has been reported to benefit patients with severe CU that is steroid dependent and not responding to other agents. It is used at a high dose of 2 g/Kg body weight once every 4–6 weeks (Watkins et al. 2012). Its side effects at this high dose include headaches, aseptic meningitis, hypertension, and others.

Omalizumab

Omalizumab is a recombinant DNA derived IgG1kappa humanized antibody. It binds to free serum IgE to the Fc domain that binds the high affinity Fc Epsilon receptor. This inhibits the binding of IgE to its receptor effectively, preventing the action of IgE. The reduction of bound IgE reducing the level of surface expression of Fc Epsilon receptor and, therefore, reduces the effects of IgE. It is only FDA approved for use in patients 12 years of age or older who have severe steroid-dependent allergic bronchial asthma. It is not approved for use in other IgE-mediated allergic indications. There have been, however, multiple case reports demonstrating its benefit for patients with severe CU. Further studies are going on to show its effects/benefits for CU patients and procure FDA approval for this indication (Maurer et al. 2011). The drawbacks to the use of omalizumab, however, include the need to administer it in a physician's office equipped to deal with possible anaphylaxis from the medication. The drawbacks also include the need for observation after administering the medication and the local pain at the site of administration (subcutaneous). Other side effects include headaches, pharyngitis, and the possibility of development of serum sickness.

Cross-References

- Basophils
- IgE Receptor
- IgE Testing
- Mast Cell Mediators
- Mast Cells
- Mast Cells, Growth and Development
- Oral Antihistamines
- Oral Mast Cell Stabilizers

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Immunomodulator Therapy of Hypereosinophilic Syndrome

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Synonyms

Eosinophilia; HES

Definition

Hypereosinophilic syndrome (HES) is a disorder that had multiple definitions over the years. The original diagnostic criteria were formulated by Chusid (Chusid et al. 1975). Those criteria called for an elevation of eosinophils to >1,500/μl for a period of 6 months, associated with organ damage, in the absence of other causes of eosinophilia. Waiting that long, however, would prove fatal or disabling to the patients. Since then many definitions have been proposed. The current consensus diagnostic criteria divide the nomenclature of eosinophil elevation into three levels. The first is *eosinophilia* in which the eosinophil count is >500/μl and <1,500/μl. The second is *hypereosinophilia* in which the eosinophil count is >1,500/μl on two separate occasions (with an interval between the two exams of >1 month) with or without tissue hypereosinophilia and without associated organ damage and/or:

1. Bone marrow eosinophils representing 20 % of the total marrow cellularity and/or
2. Extensive tissue infiltration by eosinophils as determined by the judgment of a pathologist and/or
3. Abnormal and extensive deposition of the eosinophil granule proteins in the tissues

The third is *hypereosinophilic syndrome* in which the criteria for hypereosinophilia are fulfilled and the organ involvement by eosinophils results in damage or dysfunction. The damage or dysfunction has to be a result of eosinophils and occur in the absence of other diseases that can cause eosinophilia or organ damage (Valent et al. 2012).

Immunomodulator Therapy

Initial therapies for HES included the use of systemic corticosteroids which remain as the gold standard for initial treatment and for treatment of HES in children (van Grotel et al. 2012). Other therapies for HES, considered steroid sparing, include hydroxyurea (Butterfield and Weiler 2012) and interferon alpha (Kiladjian et al. 2011; Butterfield and Weiler 2012). However, in patients with the Fip1-like1-Platelet-Derived-Growth-Factor-Receptor-Alpha-chain (FIP1L1-PDGFRA), also called chic-2 deletion, the mainstay of therapy is the use of imatinib mesylate (Elling et al. 2011; Helbig and Kyrcz-Krzemien 2011). Other, more recent advancement in the therapy of HES involves the utilization of humanized monoclonal antibodies against the eosinophil growth factor interleukin-5, mepolizumab (Boucher et al. 2008; Busse et al. 2010; Corren 2012) and reslizumab (Castro et al. 2011; McCallister 2011; Samitas et al. 2011; Corren 2012) or benralizumab (MEDI-563) against the receptor of interleukin-5 (Ghazi et al. 2012; Molfino 2012). Those treatments are yet to be approved by the food and drug administration (FDA). Other experimental immunomodulator therapies for eosinophilic disorders not approved for HES therapy include alemtuzumab (Gotlib 2010; Syed et al. 2012). In the experimental realm and not including monoclonal antibodies are studies using of a CCR3 antagonist (Greiff et al. 2010), or use of a CCR3 antisense mRNA

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(Gauvreau et al. 2008). CCR3 is a receptor for the eosinophil chemotactic factor eostaxin.

Hydroxyurea

Hydroxyurea was first reported to be of benefit for patients with HES by Chusid (Chusid and Dale 1975). It is a cell cycle specific antineoplastic agent. It is approved by the FDA for use in multiple hematologic disorders and solid organ malignancies as outlined in Micromedix. There is a plethora of literature since the first report showing its benefit in some HES patients as a steroid-sparing agent. It can be used alone or in combination with other agents or systemic steroids. Its side effects, however, include myelosuppression, as well as hepatic and renal toxicity. It can also cause hyperuricemia. Therefore, while a patient is on therapy with hydroxyurea, the clinician should monitor the patient at appropriate intervals with a complete blood count with differential, liver enzymes, serum creatinine, serum uric acid and a urinalysis with microscopy. It should be discontinued at the onset of any toxicity or if the patient is unable to tolerate it.

Interferon Alpha

Interferons are a group of biologic immunomodulating agents that have been classified into two groups. The first group includes interferon alpha and beta, while the second group includes interferon gamma. Recombinant forms of these proteins are available as therapeutic agents for different indications. Interferon alpha is indicated for use in viral liver infections, AIDS-related Kaposi's sarcoma, and a few hematologic and solid organ malignancies. It has a plethora of uses outlined in Micromedix that are not FDA approved. It is highly efficacious in the treatment of most patients with HES and considered one of the first-line therapeutic steroid-sparing agents. Its clinical side effects include influenza-like symptoms the day of and after administration, possible development of severe depression that can be recalcitrant to antidepressants, and hypothyroidism. It laboratory side effects include hepatotoxicity and myelosuppression. It is administered subcutaneously by the patient 3 days a week. A pegylated form of interferon (PEG interferon) has a much longer half-life and is used once a week. PEG interferon is as efficacious as regular interferon but much more expensive (Butterfield and Weiler 2012). If a patient is treated with interferon, it can be used as a single agent or in combination with steroids or other agents. The patient should be aware of the side effects and monitored very closely, both for the clinical and laboratory side effects. This includes laboratory studies to evaluate the liver enzymes, complete blood count and differential, thyroid function, and serum creatinine.

Imatinib Mesylate

Imatinib is a second-generation tyrosine kinase inhibitor. It is indicated for Philadelphia chromosome–positive chronic myeloid leukemia. It is extremely efficacious as a therapeutic agent for a small subgroup of HES patients. This is the subgroup that harbors the FIP1L1-PDGFRA mutation, otherwise referred to as chic-2 deletion. It is an oral medication that can be started at the recommended dose and once the eosinophil count becomes normal, the dose can be reduced to the minimal effective dose. Side effects include edema, rashes, weight gain or loss, nausea, vomiting and diarrhea, headaches, throat pain, and fatigue. Serious side effects include cardiac tamponade (very rare), severe dermatologic rashes, liver toxicity, myelosuppression, hearing loss, gastrointestinal perforation, and/or renal failure. Patients placed on imatinib need to be followed closely clinically and by laboratory studies that should include complete blood count and differential, liver enzymes, serum creatinine, and electrocardiograms.

Monoclonal Antibodies

The only monoclonal antibody available clinically, for indications other than HES, is alemtuzumab. It is an anti-CD 52 antibody. There are case reports showing its successful use as a therapeutic agent for HES when other therapies fail. The rationale for its use is the expression of CD 52 on the surface of eosinophils. Its side effects include hypotension, rashes, nausea, vomiting and

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diarrhea, myelosuppression, asymptomatic viremia with cytomegalovirus, generalized aches, and pains as well as anxiety. The serious reported side effects include arrhythmias, severe myelosuppression, severe viral infections resulting in death, demyelinating disorders, toxic optic neuropathy, Goodpasture's syndrome, graft-versus-host disease, and fatal transfusion reactions. It is therefore reserved for patients with severe life-threatening complications from HES. It is administered intravenously in an observed setting.

Other monoclonal antibodies are in the experimental realm. The one most tested for HES is mepolizumab, an anti-IL-5 antibody. The other anti-IL-5 antibody is reslizumab which has been studied for other eosinophilic disorders. Benralizumab (MEDI-563), an anti-IL-5 receptor antibody, has not been evaluated as a therapeutic agent for HES.

Other Experimental Therapies

Other experimental therapies have been tested for eosinophilic disorders other than HES. They include agents against the receptor for the eosinophil chemotactic factor eotaxin, namely, CCR3. One agent is effective pharmacologically and the other is an antisense mRNA. Both agents are in the early clinical testing stages.

Cross-References

- Eosinophil Activation
- Eosinophil, Definition and Morphology
- Eosinophil Granule Proteins
- Eosinophil Historical Background
- Eosinophil Progenitors, Growth, and Differentiation and Death
- Eosinophil Receptor Expression
- Eosinophil Recruitment
- Eosinophilic Gastrointestinal Disorders

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Immunomodulator Therapy of Mastocytosis

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Synonyms

Indolent systemic mastocytosis; Smouldering systemic mastocytosis; Systemic mastocytosis

Definition

Mastocytosis is a hematologic myeloproliferative disorder characterized by abnormal clonal expansion of mast cells. For its diagnosis, one major and one minor criteria are needed or three minor criteria are needed. The major criterion is multifocal extracutaneous accumulation of 15 or mast cells. The four minor criteria include: abnormal mast cell morphology, abnormal expression of CD2 or CD25 on the surface of mast cells, serum tryptase level at or above 20 ng/mL, and the presence of Kit-Asp816Val mutation (Arock and Valent 2010). There are different types of mast cell disorders. They include: cutaneous mastocytosis, systemic mastocytosis (indolent, smouldering, and aggressive varieties), systemic mastocytosis with an associated hematologic clonal non-mast cell lineage disease (AHNMD), mast cell leukemia, and mast cell sarcoma (Pardanani 2012).

Immunomodulator Therapy

The therapy of mastocytosis is dependent on the patient's symptoms, the extent of bone marrow involvement, and the presence of other hematologic disorders. Some patients are asymptomatic in which case the most important medication is to provide them with an epinephrine autoinjector and educate them on its use. Others have symptoms of mast cell activation; these include flushing, itching, diarrhea, abdominal pain, hypotension, and in some progress to anaphylaxis. The symptoms of mast cell mediator release can be either blocked or attenuated with type 1 and type 2 antihistamines, leukotriene antagonists, and mast cell stabilizers. Some patients, however, experience recurrent anaphylaxis (Wimazal et al. 2012). Others have mast cells involving more than 20 % of their bone marrow cellularity, organ infiltration by mast cells (B-findings), and organ dysfunction secondary to mast cell infiltration (C-findings) (Pardanani 2012).

Patients with recurrent anaphylaxis, smouldering systemic mastocytosis, aggressive systemic mastocytosis, mast cell leukemia, and mast cell sarcoma require cytoreductive immunomodulator therapy. Those therapies are tailored to the specific needs of the patient. Other patients with systemic mastocytosis and AHNMD should receive tailored treatment for each condition, as the co-occurrence of both disorders does not influence the treatment. The immunomodulator therapies include the following:

Tyrosine Kinase Inhibitors

Imatinib mesylate: Imatinib mesylate is a new-generation tyrosine kinase inhibitor. It binds to the second activation intracellular kinase domain of the mast cell growth receptor Kit. It only works for patients with mastocytosis who *do not* have the Kit Asp816Val mutation, which also affects the second intracellular kinase domain of Kit. If the Kit Asp816Val mutation is present, then the binding site of imatinib is lost and it becomes no longer efficacious.

Other tyrosine kinase inhibitors that might have some efficacy against the most common mutation in mastocytosis (Kit Asp 816Val) are under study. Those include, but are not limited to, *PKC412* (*midostaurin*) and *masitinib*. Preliminary studies show some efficacy of those two inhibitors against mast cells with the Kit

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Asp816Val mutation. Previous studies using dasatinib for treatment of patients with the Kit Asp816al mutation did not show much success (Ustun et al. 2011).

Interferon Therapy

Interferons were discovered over 50 years ago after identification of their antiviral activity. Subsequent studies showed that there are different types of interferons. Those types are divided into two categories. The first one includes interferons alpha and beta and the second, interferon gamma. Interferon alpha is currently available in recombinant form and is FDA approved for the treatment of Hepatitis B and C infections as well as the treatment of myeloid malignancies. The WHO classified systemic mastocytosis as a myeloid malignancy in the 2008 revision of the mastocytosis diagnostic criteria (Kiladjian et al. 2011). The efficacy of interferon alpha therapy for patients with systemic mastocytosis has been reported over the years in small case reports. There are no large double-blind placebo-controlled studies evaluating the efficacy of interferon for mastocytosis patients. This is likely multifactorial: First, the disease is rare; second, it is unethical to use a placebo in patients requiring cytoreductive therapy; and finally, the side effects of interferon will prevent blinding the patient and the investigator. Another benefit that interferon imparts on patients with mastocytosis and bone fractures is the restoration of bone density. The main side effects of interferon include influenza-like symptoms with or without development of depression that can be disabling to some patients. The major toxicity is hepatotoxicity, but myelosuppression can occur.

Cladribine (2-chlordeoxyadenosine, 2-CDA)

Cladribine (or 2-chlorodeoxyadenosine) is a purine analog that interferes with cell division. Many case reports show its efficacy in therapy of some patients with mastocytosis who failed interferon therapy, or those with aggressive mastocytosis who need rapid debulking of the mast cell load. Its main side effect is myelosuppression (Pardanani 2012).

Cross-References

- Hyper-IgE Syndrome
- Immunomodulator Therapy of Hypereosinophilic Syndrome
- Insect Allergy in Children
- Mast Cell Mediators
- Mast Cells, Growth and Development
- Mastocytosis

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Immunotherapy for Allergic Rhinitis

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Synonyms

Allergen immunotherapy; Allergen-specific desensitization; Allergic rhinitis; Allergy immunotherapy; Allergy injections; Allergy shots; Hay fever; Hyposensitization; Immunotherapy

Definition

Immunotherapy for allergic rhinitis involves the long-term administration of specific environmental allergens to individuals sensitized to these allergens through IgE-mediated mechanisms for the purpose of diminishing or eliminating the allergic symptoms caused by exposure to these allergens (Cox et al. 2011).

Background

Allergic rhinitis affects an estimated 600 million individuals worldwide, including 200 million individuals with associated asthma (Calderon et al. 2011). Individuals who have allergic rhinitis have symptoms such as nasal discharge, nasal congestion, nasal itching, sneezing, and/or postnasal drainage (Nelson 2009). Many people with allergic rhinitis have symptoms that can be satisfactorily controlled with readily available medications such as antihistamines and nasal corticosteroid sprays. However, about 20 % of these individuals with allergic rhinitis have more severe disease that does not respond adequately to pharmacologic therapies. Other individuals may respond to various medications but opt to pursue a more curative approach for their allergic rhinitis. These groups of patients can benefit from allergy immunotherapy (Calderon et al. 2011).

Clinical Indications

Immunotherapy should be considered for individuals who demonstrate evidence of allergic sensitization through specific IgE antibodies to relevant environmental allergens and also have symptoms of allergic rhinitis when naturally exposed to these allergens. The decision to choose immunotherapy as a treatment option depends on several factors including the severity and duration of symptoms, responsiveness to medication and avoidance measures, adverse effects of medications, and an individual's treatment preference. Candidates for immunotherapy typically have symptoms not controlled by either medications or avoidance measures, experience unacceptable adverse side effects from medications, and/or prefer to reduce the long-term use of medications (Cox et al. 2011).

Efficacy

Immunotherapy has demonstrated significant beneficial effects for the treatment of allergic rhinitis in a number of placebo-controlled randomized clinical trials. These trials have shown that immunotherapy is effective in both adults and children for the treatment of a variety of environmental allergens including pollen, fungi, animal allergens, dust mites, and cockroaches. Outcome measures used to demonstrate the efficacy of immunotherapy include symptom and medication scores, allergen challenges, and immunologic changes in cell markers and cytokine profiles (Cox et al. 2011).

A meta-analysis of 16 prospective, blinded, placebo-controlled studies of immunotherapy for allergic rhinitis published between 1966 and 1996 found that in 15 (94 %) of the 16 studies, active treatment with immunotherapy was effective. Allergic rhinitis symptoms were more likely to improve in patients receiving immunotherapy than in comparison patients with an odds ratio of 1.81. Symptom scores and medication usage were significantly lower in those receiving immunotherapy in all studies that employed

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such outcome measures (Ross et al. 2000). A larger and more recent meta-analysis of 51 randomized, double-blind, placebo-controlled trials of immunotherapy for seasonal allergic rhinitis published from 1981 to 2006 also found immunotherapy treatment to be effective with significant reductions in symptom scores and medication use compared to placebo. These immunotherapy benefits translated into clinically and statistically significant improvements in rhinitis quality of life scores as well. These trials also demonstrated that immunotherapy resulted in favorable immune responses with significant increases in specific IgG levels and in specific IgG4 levels compared to placebo (Calderon et al. 2007).

Immunotherapy for allergic rhinitis may have long-term persistent benefits after immunotherapy is discontinued. Immunotherapy may also prevent the development of new allergic sensitizations and reduce the risk for the future development of asthma in some patients with allergic rhinitis (Cox et al. 2011).

Cross-References

- ▶ Allergen Immunotherapy, Overview
- ▶ Immunotherapy for Asthma
- ▶ Immunotherapy for Hymenoptera Allergy
- ▶ Immunotherapy, Mechanisms
- ▶ Immunotherapy with Recombinant and DNA-Conjugated Allergens
- ▶ Safety of Immunotherapy
- ▶ Sublingual Immunotherapy

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Immunotherapy for Asthma

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Synonyms

Allergen immunotherapy; Allergen-specific desensitization; Allergy immunotherapy; Allergy injections; Allergy shots; Asthma; Hyposensitization; Immunotherapy

Definition

Immunotherapy for asthma is the repeated administration of specific allergens to individuals who are sensitized to these airborne environmental allergens through IgE-mediated mechanisms for the purpose of reducing or eliminating the allergic symptoms due to exposure to these allergens (Cox et al. 2011).

Background

Asthma affects all ages, races, and ethnicities, affecting an estimated 300 million people worldwide with 250,000 deaths annually attributed to the disease (World Health Organization 2007). Significantly, half of all adults with asthma and at least two thirds of children with asthma have allergies (Calderon et al. 2011). Allergens may

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contribute to the development of asthma, cause respiratory exacerbations, and contribute to airway inflammation with subsequent clinical symptoms (Boulet 2009). Thus, adequately treating underlying allergies and reducing allergen responses is one of many therapeutic considerations in the treatment of asthma.

Clinical Indications

Immunotherapy should be considered for individuals with asthma who demonstrate evidence of IgE-mediated sensitization to relevant environmental allergens and have symptoms of asthma after natural exposure to these allergens. The decision to begin immunotherapy depends on several factors including symptom severity, efficacy of medication and avoidance measures, medication side effects, and an individual's treatment preference (Cox et al. 2011).

Efficacy

Immunotherapy has demonstrated significant beneficial effects for the treatment of asthma in a number of randomized controlled clinical trials. These trials have shown that immunotherapy is effective in both adults and children for the treatment of a variety of environmental allergens including pollen, fungi, animal allergens, and dust mites (Cox et al. 2011). A meta-analysis was conducted including 88 randomized controlled trials of immunotherapy for asthma involving 3,459 asthmatic patients. There were 42 trials of immunotherapy for house dust mite, 27 for pollen, 10 for animal dander, 2 for *Cladosporium* mold, 2 for latex, and 6 for multiple allergens. Overall, there were significant reductions in asthma symptoms, medication use, and bronchial hyperreactivity to both allergenic and nonspecific stimuli. This meta-analysis determined that it would have been necessary to treat three patients (95 % CI 3–5) with immunotherapy to avoid one deterioration in asthma symptoms. In addition, it would have been necessary to treat four patients (95 % CI 3–6) with immunotherapy to avoid one patient requiring increased medication (Abramson et al. 2010).

Special Precautions

Immunotherapy for asthma should not be initiated unless an individual's asthma is stable and under control. Patients with severe or uncontrolled asthma have an increased risk for systemic reactions when receiving immunotherapy injections. Moreover, fatal and near-fatal reactions from immunotherapy injections were found to be more common in those with severe asthma. An assessment of a patient's asthma control should be performed prior to each immunotherapy injection (Cox et al. 2011).

Cross-References

- Allergen Immunotherapy, Overview
- Immunotherapy for Allergic Rhinitis
- Immunotherapy for Hymenoptera Allergy
- Immunotherapy, Mechanisms
- Immunotherapy with Recombinant and DNA-Conjugated Allergens
- Safety of Immunotherapy
- Sublingual Immunotherapy

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Immunotherapy for Hymenoptera Allergy

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Synonyms

Allergen immunotherapy; Allergen-specific desensitization; Allergy immunotherapy; Allergy injections; Allergy shots; Hyposensitization; Immunotherapy; Insect allergy; Stinging insect allergy

Definition

Immunotherapy for Hymenoptera allergy is the repeated administration of specific insect venom protein allergens to individuals who are sensitized to these allergens through IgE-mediated mechanisms for the purpose of preventing systemic allergic reactions due to exposure to these allergens from stinging insects (Cox et al. 2011).

Background

The order Hymenoptera comprises a number of stinging insects which can cause allergic reactions. Three families of stinging insects of particular importance in allergy are Apidae, Vespidae, and Formicidae. Representatives of these three families include Apidae (honeybee), Vespidae (yellow jacket, yellow hornet, white-faced hornet, paper wasp), and Formicidae (fire ant). Insect sting allergy can occur at any age with systemic allergic reactions reported in up to 3 % of adults and almost 1 % of children. Almost all systemic insect sting reactions are IgE mediated and cause anaphylaxis. Fatal insect sting reactions occur about 40 times each year in the United States. Venom immunotherapy is considered the treatment of choice for the prevention of systemic allergic reactions to insect stings (Golden 2009).

Clinical Indications

Immunotherapy should be considered for individuals who have a history of systemic reactions to Hymenoptera stings, especially when associated with respiratory or cardiovascular symptoms, and who demonstrate evidence of venom-specific IgE antibodies. In the United States, individuals older than 16 years who experience a systemic reaction limited to the skin are also candidates for immunotherapy. Individuals 16 years or younger who only have cutaneous reactions to Hymenoptera stings might not require immunotherapy (Cox et al. 2011).

Insect stings may also cause large local reactions which can result in significant morbidity and impair quality of life. There is evidence that venom immunotherapy might significantly reduce the size and duration of large local reactions and may be of benefit in individuals with frequent and disabling large local reactions, particularly those with occupational exposure (Cox et al. 2011).

Efficacy

Immunotherapy has been demonstrated to be effective for the prevention of allergic reactions to insect stings in a number of randomized controlled clinical trials. In a number of studies, venom immunotherapy has been shown to be 95–100 % effective in preventing systemic sting reactions. Even in cases considered to be treatment failures, subsequent, repeated sting reactions are generally milder than reactions prior to immunotherapy treatment (Golden 2009).

A meta-analysis was conducted including six randomized controlled trials of venom immunotherapy for preventing further allergic reactions in individuals who had experienced an allergic reaction. The interventions included 392 participants and included bee, wasp, and ant

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immunotherapy in adults or children with previous systemic or large local reactions to a sting. In the trials, 2.7 % of participants treated with venom immunotherapy had a subsequent systemic allergic reaction to a sting, compared to 39.8 % of participants who were untreated (risk ratio [RR] 0.10, 95 % confidence interval [CI] 0.03–0.28). Venom immunotherapy was also found to be effective for preventing large local sting reactions (RR 0.41, 95 % CI 0.24–0.69) and for improving quality of life (Boyle et al. 2012).

Duration

Published studies collectively suggest that venom immunotherapy may be discontinued after 5 years of treatment in most individuals. Possible exceptions include those treated for honeybee allergy, those who had a systemic reaction to a sting or to an immunotherapy injection during venom immunotherapy, and those who had very severe sting reactions before immunotherapy treatment. These exceptions may lead to continued treatment of more than one-third of the patients receiving venom immunotherapy. After stopping immunotherapy, there is an approximately 10 % chance of a systemic reaction with each sting, with a cumulative relapse risk between 15 % and 20 %. Long-term extension of treatment may be considered by individuals who find this relapse risk unacceptable (Golden 2009).

Special Considerations Regarding Tryptase and Mastocytosis

For individuals with moderate or severe anaphylactic reactions to insect stings, a measurement of a baseline serum tryptase level is recommended. Increased tryptase levels are associated with more frequent and more severe anaphylactic sting reactions as well as greater immunotherapy failure rates and greater relapse rates after immunotherapy is discontinued. In addition, an increased baseline serum tryptase level is also an indicator for a possible clonal mast cell disorder, including mastocytosis (Cox et al. 2011). Therefore, individuals who have systemic reactions, especially anaphylaxis, after Hymenoptera stings and who have increased baseline serum tryptase levels should be considered to undergo a bone marrow examination for evaluation of clonal mast cell disease (Bonadonna et al. 2009). Patients with mastocytosis have a much higher incidence of severe anaphylaxis from Hymenoptera stings than the general population. With venom immunotherapy, most patients with mastocytosis are protected from further allergic sting reactions. Thus, immunotherapy for life is recommended for individuals with mastocytosis and Hymenoptera allergy (Bonadonna et al. 2010).

Special Precautions

A greater risk of more severe reactions from venom immunotherapy has been associated with the use of angiotensin-converting enzyme (ACE) inhibitor medication. Discontinuation of ACE inhibitors should be considered for patients receiving venom immunotherapy. If ACE inhibitor therapy is required and no alternative therapy is available, then immunotherapy should be carefully considered from an individual patient's risk/benefit standpoint (Cox et al. 2011).

Cross-References

- ▶ Allergen Immunotherapy, Overview
- ▶ Immunotherapy for Allergic Rhinitis
- ▶ Immunotherapy for Asthma
- ▶ Immunotherapy, Mechanisms
- ▶ Immunotherapy with Recombinant and DNA-Conjugated Allergens
- ▶ Safety of Immunotherapy
- ▶ Sublingual Immunotherapy

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Immunotherapy with Recombinant and DNA-Conjugated Allergens

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Synonyms

Allergen immunotherapy; Allergen-specific desensitization; Allergy immunotherapy; Allergy injections; Allergy shots; Hyposensitization; Immunotherapy

Definition

Recombinant technology and DNA-conjugated allergens are being developed and studied as an effort to have safer and more effective forms of immunotherapy (Cox et al. 2011).

Background

Despite the benefits of conventional subcutaneous immunotherapy, not all individuals improve, and the risk of adverse reactions, such as anaphylaxis, remains. Thus, safer and more effective forms of immunotherapy are needed (Casale and Stokes 2011).

Strategies to improve immunotherapy are utilizing recombinant technologies. Most clinically important allergens have been identified, cloned, sequenced, and expressed in a variety of systems. This knowledge allows a number of possibilities including expression of allergenic proteins in fragments, expression of only limited portions of the protein as peptides, or mutation or deletion of specific amino acids within the protein or its component peptides (Nelson 2009). Recombinant allergens can then be produced which mimic the properties of the natural allergen, which reduce allergenic activity, or which increase immunogenicity (Casale and Stokes 2011). Recombinant allergens have been used in clinical trials as forms of immunotherapy themselves and as conjugates to immunostimulatory oligonucleotide sequences of DNA containing a CpG motif (Cox et al. 2011). Nucleotide sequences of unmethylated CpGs are found commonly in bacterial DNA but are suppressed and methylated in eukaryotic DNA (Casale and Stokes 2011). The receptor for CpG DNA is toll-like receptor 9 (TLR9), which is found primarily on plasmacytoid dendritic cells. TLR9 can lead to the production of interleukin-10, IgG isotype switching, and inhibition of other T_H2 immune responses, thereby shifting the immune response toward T_H1 production (Cox et al. 2011).

Efficacy

Recombinant wild-type pollen allergens have been used in two studies in patients with allergic rhinitis. The first study used a mixture of five different recombinant allergens of timothy grass in a randomized, double-blind, placebo-controlled trial in 62 patients. Treatment consisted of subcutaneous injections for 18 months, and patients receiving recombinant therapy had a 36 % decrease in both symptoms and medication use during the grass season when compared to placebo. Systemic reactions occurred in about 1 % of recombinant grass allergen injections. The second study compared recombinant birch pollen allergen vaccine,

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standard birch pollen extract, natural purified birch pollen allergen, and placebo in a randomized, double-blind, placebo-controlled trial in 134 patients with birch allergy. Treatment consisted of subcutaneous injections for 2 years, and all three actively treated groups had equal improvements in symptoms, medication use, and skin test reactivity during the pollen seasons when compared to placebo (Casale and Stokes 2011).

A CpG immunostimulatory DNA conjugate with ragweed allergen Amb a 1 (trade name TOLAMBA; Dynavax Technologies, Berkeley, CA) has been studied in a randomized, double-blind, placebo-controlled phase 2 trial in 25 adults with ragweed-induced allergic rhinitis. TOLAMBA was administered in six increasing doses before the ragweed season. The TOLAMBA group demonstrated a significant reduction in total nasal symptom scores during the peak season when compared to placebo. A subsequent larger trial with TOLAMBA was discontinued after an interim analysis indicated that neither the placebo nor the CpG groups had symptoms during the ragweed season; thus, no efficacy data could be measured (Cox et al. 2011).

Conclusion

Recombinant allergens and CpG DNA-conjugated allergens show promise and potential as novel and effective future forms of immunotherapy. However, more study is needed for these formulations before they can be considered as standard and safe therapeutic options.

Cross-References

- Allergen Immunotherapy, Overview
- Immunotherapy for Allergic Rhinitis
- Immunotherapy for Asthma
- Immunotherapy for Hymenoptera Allergy
- Immunotherapy, Mechanisms
- Safety of Immunotherapy
- Sublingual Immunotherapy

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Immunotherapy, Mechanisms

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Synonyms

Allergen immunotherapy; Allergen-specific desensitization; Allergy immunotherapy; Allergy injections; Allergy shots; Hyposensitization; Immunotherapy

Definition

Allergic diseases are considered to result from immune dysregulation, probably T-cell regulated, in the normal immune tolerance typically seen with natural exposure to allergens. Through the administration of specific allergens to individuals who are sensitized to these allergens through IgE-mediated mechanisms, immunotherapy can induce specific clinical and immunologic tolerance, resulting in clinical improvement in symptoms and altering the natural history of the allergic disease (Calderon et al. 2011). Immunologic changes associated with immunotherapy are complex, and the specific mechanisms responsible for its efficacy are becoming better understood (Cox et al. 2011).

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Immunologic Responses to Immunotherapy

An early event of immunotherapy, occurring within days or weeks, is the generation of a population of regulatory T cells, which are $CD4^+CD25^+$ T lymphocytes. These regulatory T cells can produce inhibitory cytokines, such as IL-10 and TGF-β. IL-10 has several properties including induction of a decrease in B-cell antigen-specific IgE production and increased IgG4 levels; a reduction in proinflammatory cytokine release from mast cells, eosinophils, and T cells; and elicitation of T-cell tolerance by selective inhibition of the CD28 costimulatory pathway. These properties result in reduced lymphoproliferative responses to allergen after immunotherapy. With continued immunotherapy, an allergen-specific immune deviation from a T_H2 to a T_H1 cytokine response to the administered allergen predominates (Cox et al. 2011).

The immunologic response to immunotherapy is characterized by decreased sensitivity in end organs and by changes in the humoral and cellular responses to administered allergens. Responses to allergen challenges, including both immediate and delayed responses, are reduced in the conjunctiva, skin, nasal mucosa, and bronchi. Immunotherapy also decreases allergen-induced eosinophil, basophil, and mast infiltration. Blunting of mucosal priming and reduction of nonspecific sensitivity to bronchoconstrictive agents are additional changes induced by immunotherapy (Cox et al. 2011).

Other immunologic changes which occur during immunotherapy include an initial increase in specific IgE antibody levels, followed by a gradual decrease in IgE levels toward to or less than baseline levels. Serum allergen-specific levels of IgG1, IgG4, and IgA all increase with immunotherapy. Allergen-specific IgG can block IgE-dependent histamine release and IgE-facilitated antigen presentation to T cells. However, none of these changes in antibody levels have consistently correlated with clinical improvement (Cox et al. 2011).

Conclusion

As the mechanisms of immunotherapy are better elucidated, more effective and safer forms of immunotherapy can be developed, thus improving an already effective mode of therapy for allergic diseases.

Cross-References

- ▶ Allergen Immunotherapy, Overview
- ▶ Immunotherapy for Allergic Rhinitis
- ▶ Immunotherapy for Asthma
- ▶ Immunotherapy for Hymenoptera Allergy
- ▶ Immunotherapy with Recombinant and DNA-Conjugated Allergens
- ▶ Safety of Immunotherapy
- ▶ Sublingual Immunotherapy

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Imported Fire Ant Allergy

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Synonyms

Solenopsis invicta; *Solenopsis richteri*

Definition

Imported fire ants are species of ants not native to the United States. Allergy refers to the fact that

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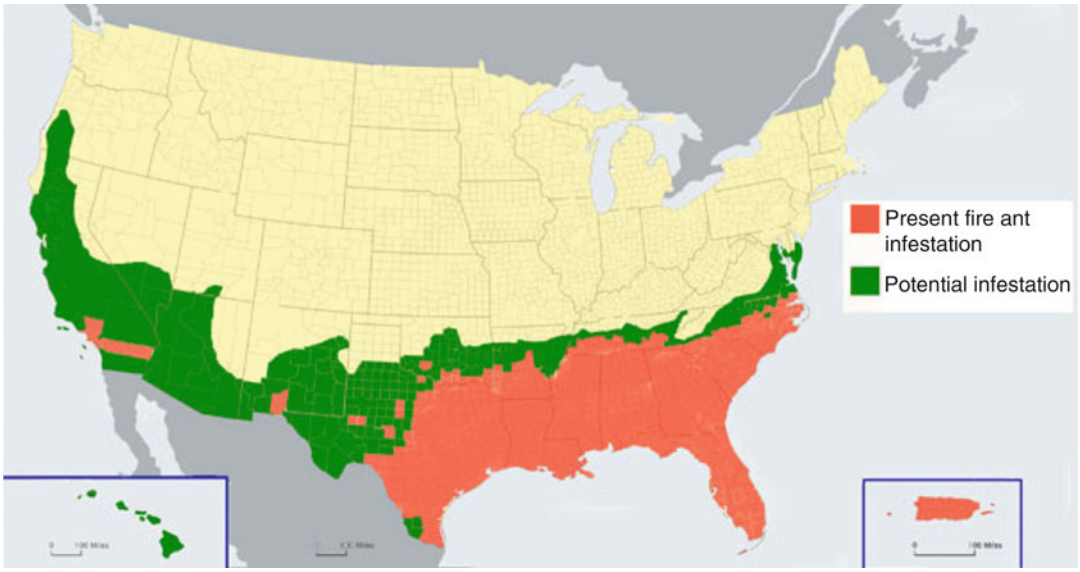


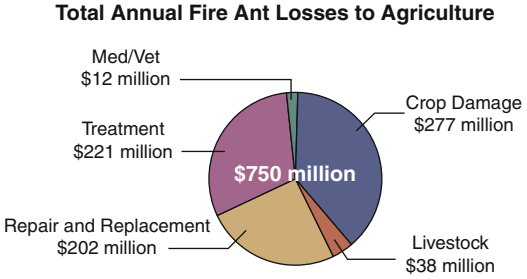
Imported Fire Ant Allergy, Fig. 1 Current and Potential US imported fire ant infestation (http://www.ars.usda.gov/fireant/imported.htm)

some foreign proteins (antigens) induce a type 1 (Gell and Coombs) immunologic response that produces specific immunoglobulin E. When this immunoglobulin is cross-linked on the surface of mast cells by the antigen, mediators are released producing clinical symptoms termed an allergic response.

Introduction

Imported fire ant (IFA) refers to members of 2 species of fire ants, *Solenopsis invicta* and *Solenopsis richteri*. These species are native to different areas along the Platte River and its tributaries in South America and were "imported" into the United States in the early 1900s, *S. richteri* first then *S. invicta*. There are native fire ant species in the United States, but these have not had the medical impact of the IFA species. The importation occurred through the port of Mobile, Alabama. The current area of infestation is seen on a map from the US Department of Agriculture (Fig. 1).

The importation of these omnivorous species without their native biologic controls has resulted



Imported Fire Ant Allergy, Fig. 2 Total annual fire ant losses to agriculture (http://www.ars.usda.gov/fireant/imported.htm)

in their rapid spread and in significant economic impact. IFA have had some beneficial effects by decreasing pest species like sugar cane borers and ticks (Lofgren et al. 1975), but damage to crops, livestock, and infrastructure has far outweighed these effects. The USDA estimates the annual yearly economic impact as over five billion dollars (see Figs. 2 and 3).

The story of the attempt to control IFA is an interesting one. Initially, large areas were treated with insecticides like Mirex. The failure of this to control IFA was documented in Rachel Carson's book Silent Spring (Carson 1962). The Fire Ant Wars (Buhs 2002) is a study of the interaction

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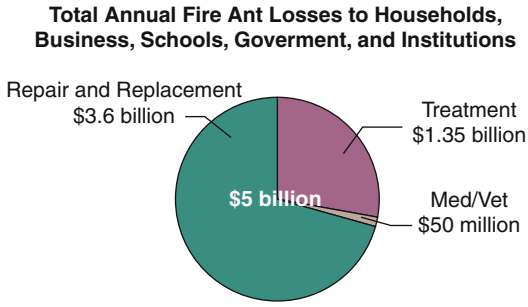

Imported Fire Ant Allergy, Fig. 3 Total annual fire ant losses to households, business, schools, government, and institutions (http://www.ars.usda.gov/fireant/imported.htm)

between science, culture, and government in attempting to control IFA. The current plan for control involves the introduction of additional species such as the phorid fly (Psuedacteon species), which requires IFA in order to propagate, and microsporidium (Kneallhazia species) that are obligate parasites of IFA. These species are apparently decreasing the density of IFA infestations and thus the overall economic impact.

Entomology

IFA have some unusual behaviors that impact their medical importance. First stinging events are most likely to occur when disturbing one of their mounds. Such disturbance will cause hundreds to thousands of ants to respond and the usual stinging event results in stings from multiple individual fire ants. Each ant when stinging will grasp the victim with their mandible and arch their abdominal segment and insert their stinger to inject venom. If not physically removed, the ant will remove their stinger, rotate their thorax and abdominal segments slightly, and inject again. This results in several stings occurring in an arch like pattern. See Fig. 4.

The majority of the venom (~95 %) consists of dialkylpiperidines. After a sting event, the typical response is almost immediate burning with local redness and swelling. Over the next 24 h, a 1–2 mm blister will form at the site of the sting that fills with a cloudy cellular material. While this resembles a pustule (implying an infection), it is not. Since the venom has been shown to have insecticidal, bactericidal, and fungicidal activity (Lofgren et al. 1975), and the piperidines have been shown to directly activate platelets and neutrophils (Javors et al. 1993), this has been called a pseudopustule. Over the next week, this lesion will resolve, sometimes leaving a small hypo- or hyperpigmented scar. The pseudopustule may remain itchy until it resolves.

The venom does contain some protein components, although the usual protein content per sting is 10–100 ng for fire ants compared to 1.7–50 ug for other Hymenoptera species (Hoffman 1993a). *Solenopsis invicta* has been shown to contain 4 protein components and *Solenopsis richteri* has been show to contain 3 protein components. Conventionally, these are labeled Sol i 1, 2, 3, and 4 and Sol r 1, 2, and 3. Sol r 1, 2, and 3 appear homologous to Sol i 1, 2, and 3, respectively (Hoffman et al. 1989). Sol i 1 is a lipase and appears to be responsible for cross-reactivity between IFA and other Hymenoptera (Hoffman 2005). Sol i 2 and 4 appear similar to each other but different from other Hymenoptera venoms (Hoffman 1993a). Sol i 3 appears to be like wasp antigen 5 but does not cross-react with wasp venoms (Hoffman 1993b). These venom components are responsible for the development of specific IgE in patients that leads to the clinical manifestations of IFA allergy discussed below.

Clinical Presentation

In endemic areas, IFA may have a very high sting attack rate in those involved in outdoor activities of up to 51 % (Tracy et al. 1995). In endemic areas, IFA may account for many of the acute evaluations after stings by arthropods (48 %) (Adams and Lofgren 1982) and most of the immunotherapy for insect sting allergy (59 %) (Freeman 1997). Clinically significant events have been reported in other areas of the world including Asia and Australia (Shek et al. 2004; Wong and Yeun 2005) and Spain (Fernandez-Melendez et al. 2007).

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Imported Fire Ant Allergy, Fig. 4 Note grouping of pseudopustules at arrowhead

The usual clinical presentation is outlined above under entomology. This does not involve a specific immune response and is only clinically significant if the sterile pseudopustule is accidentally or purposefully opened. If this occurs, then secondary infection is more likely and can lead to morbidity without involving an allergic response (Triplett 1976).

After an exposure to IFA, up to 20–25 % of adults will develop specific IgE to one or more of the venom components. This rate may be even higher in children (Patridge et al. 2008). If a patient has specific IgE to IFA venom, when they are subsequently exposed, they have a risk of a more severe reaction.

One group of patients may develop what is termed large local reactions. This involves progressive enlargement of the area of swelling around the sting site that may not peak until 2–3 days later and may take a week to resolve. The area involved can be extensive and may involve swelling of a whole limb from a sting on a digit. After a large local reaction, future stings often produce a similar reaction but only rarely (10 %) go on to develop systemic symptoms as below (Tankersley 2008).

Of more concern are those patients that develop anaphylaxis. Anaphylaxis is a term applied to systemic allergy reactions when specific IgE is cross-linked on the surface of mast cells leading to mast cell activation and immediate release of mediators that lead to vascular leak, vasodilatation, and bronchoconstriction. This leads to symptoms which may include urticaria and angioedema, asthma, hypotension, tachydysrhythmias, abdominal cramping, nausea, vomiting, diarrhea, loss of consciousness, and seizures. Such reactions to IFA have caused fatalities (Rhoades et al. 1989). Counterintuitively, future sting events have only a 50–60 % risk of associated systemic symptoms.

Medical Therapy

Usual reactions to IFA stings do not require medical therapy, although antihistamines may help control itching. Sufferers should be cautioned not to open the pseudopustule. Large local reactions may be treated acutely with antihistamines and cold compresses. Systemic corticosteroids may minimize the peak and duration of swelling. Immunotherapy (as below) has been shown to minimize future large local reactions.

Anaphylaxis is treated acutely by epinephrine injection. Oral or injected antihistamines, inhaled beta-adrenergics, O_2, intravenous fluids, and oral or injected corticosteroids may help with specific symptoms but are not definitive care for anaphylaxis.

If a patient has suffered an anaphylactic event and has demonstrable specific IgE to IFA (either by skin testing or by in vitro methods), then immunotherapy has been shown to be an effective way to reduce future systemic reactions (Freeman et al. 1992). Immunotherapy is the delivery of an antigen to an individual with demonstrated clinical sensitivity and specific IgE antibody, in a particular manner, to reduce the risk of clinical symptoms when exposed to that antigen in the environment. Immunotherapy usually has a starting dose that is 3–5 logs smaller than the clinical dose that has provoked symptoms. Subsequently doses are given at intervals of hours to days, increasing the dose slowly until it is close to or greater than the dose expected to be seen on clinical exposure.

For other Hymenoptera-specific venom, immunotherapy is available. For IFA only

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whole body extract is available for clinical use. Immunotherapy with whole body extract for IFA has been shown to significantly reduce the risk of subsequent systemic reactions from 50–60 % down to 2–3 % (Tankersley 2008).

Cross-References

- Biting Insects (Systemic and Local Reactions)
- Honeybee Allergy
- Insect Allergy in Children
- Venom Content
- Vespid Allergy: Yellow Jackets, Hornets and Wasps

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Induction of IgE Synthesis: Cellular Interactions and Molecular Events

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Synonyms

IgE induction

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Definition

Mechanisms involved in the induction of the synthesis of IgE antibodies.

Requirements for IgE Production

Two main signals are required to induce class switch recombination (CSR) to IgE. The first signal is mediated through the interaction between a B cell presenting major histocompatibility complex (MHC) class II-associated peptides and an antigen-specific CD4+ T cell. CD40 expressed on the B cell interacts with CD154 (also known as CD40L) on the T cell (Vercelli et al. 1989). The importance of CD40 signaling for the induction of CSR is illustrated by the immunoglobulin profile of patients suffering from X-linked hyper-IgM syndrome. These individuals have mutations in the gene encoding CD40L leading to nonfunctional CD40L and impaired CD40 signaling. As a result, CSR is impaired, leading to reduced levels of circulating IgG, IgA, and IgE antibodies and elevated IgM levels (Elgueta et al. 2009; Korthauer et al. 1993).

CD40-CD40L Interaction in Class Switch Recombination

A multitude of signaling pathways are initiated in B cells upon CD40-CD40L interaction. Ligation of CD40 leads to recruitment of tumor necrosis factor receptor-associated factors (TRAF) 2, 3, 5, and 6 to its cytoplasmic tail. The role of these different TRAF molecules in CD40-mediated CSR was assessed using $CD40^{-/-}$ mice (Kawabe et al. 1994) with introduced mutant CD40 transgenes lacking binding motifs for TRAF2 (CD40deltaTRAF2), TRAF3 (CD40deltaTRAF3) and/or TRAF6 (CD40deltaTRAF6). The CSR defect in $CD40^{-/-}$ mice (defined as reduced serum IgG, IgA, and IgE and absence of splenic germinal centers) could be fully restored by WT and CD40deltaTRAF6, partially by CD40deltaTRAF2 and CD40deltaTRAF3 whereas CD40 lacking binding motifs for both TRAF2 and TRAF3 could not restore CSR at all. This demonstrates that TRAF6 recruitment to CD40 is not required for CSR whereas both TRAF2 and TRAF3 are important for CSR whereas TRAF6 is not (Jabara et al. 2002).

Recruitment of TRAF molecules to the cytoplasmic tail of CD40 leads to the activation of p38 mitogen-activated protein kinases (MAPK), phosphatidylinositol 3 (PI 3) kinase, C-Jun N-terminal kinase (JNK), extracellular signal-regulated protein kinase (ERK), phospholipase Cγ (PLCγ), and canonical as well as noncanonical NF-κB signaling. TRAF-independent CD40 signaling occurs through CD40-associated JAK3 and subsequent STAT5 activation (Elgueta et al. 2009; Quezada et al. 2004). It is clear that CD40 signaling is required for T-cell-dependent CSR and the respective roles for the distinct signaling pathways in regulation of CSR (including IgE CSR) are becoming increasingly clear. p50/NF-κB knockout ($p50^{-/-}$) mice show marked reduction of CSR to IgA, IgG3, and IgE, indicating that NF-κB signaling is required for T-cell-dependent CSR (Snapper et al. 1996). Inhibition of p38 MAPK by the specific p38 inhibitor SB203580 inhibits CD40/IL-4-dependent IgE CSR while PI 3-kinase or ERK inhibition does not have an inhibitory effect on IgE CSR. The suppressive effect of p38 MAPK inhibition is directly related to suppression of Iε GLTs (Zhang et al. 2002). This indicates that p38 MAPK is required for CD40-mediated CSR to IgE while PI 3-kinase and ERK are not. Furthermore inhibition of p38 MAPK decreases the CD40 activation of the Cε promoter by reducing CD40-mediated transactivation of NFκB. This suggests that CD40 activates p38 MAPK which in turn potentiates the ability of nuclear translocated NFkB to activate the Cε promoter (Brady et al. 2001). Interestingly, IgE levels were slightly enhanced by a PI 3-kinase inhibitor (Zhang et al. 2002). Later it was demonstrated that PI 3-kinase negatively regulates IgE production (Doi et al. 2008). Mice deficient for the p85α regulatory subunit of class IA PI 3-kinase produce higher amounts of serum IgE, and purified B cells from these

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animals secreted higher amounts of IgE compared to WT when in vitro treated with an anti-CD40 mAb and IL-4. Furthermore PI 3-kinase inhibitors wortmannin and IC87114 enhance IgE production by wild-type B cells stimulated with anti-CD40 mAb and IL-4. This supports a suppressive role of PI 3-kinase signaling on IgE production (Doi et al. 2008). JNK activity is also required for CSR to IgE as inhibition of JNK suppresses expression of mature ε transcripts. However, JNK appears to act at the level of AID activation rather than ε-germline expression since ε-germline and AID mRNA expression are not affected by JNK inhibition (Jabara and Geha 2005). Signaling through several nuclear hormone receptors that are expressed on B cells has been shown to suppress IgE production. These receptors include nuclear liver X receptors, which are constitutively expressed on peripheral B cells, and have been shown to counteract CD40/IL-4-induced IgE production through inhibition of JNK phosphorylation (Heine et al. 2009). Furthermore, retinoid-activated receptors, vitamin D receptor, and peroxisome proliferator-activated receptors inhibit IgE production (Heine et al. 2002; Ruhl et al. 2003; Worm et al. 1998).

BAFF and APRIL

The two members of the tumor necrosis factor (TNF) superfamily "B cell activating factor" (BAFF) and "a proliferation inducing ligand" (APRIL) can induce CSR to IgE, IgG, and IgA (Litinskiy et al. 2002). BAFF and APRIL both can bind to two receptors that are expressed by B cells: B cell maturation antigen (BCMA) and transmembrane activator and calcium-modulator and cytophilin ligand interactor (TACI). Signaling through these receptors leads to AID expression and, when combined with IL-4, CSR to IgE. The involvement of a third receptor that specifically binds BAFF (BAFFR) in CSR remains uncertain. It has been proposed that BAFF- and APRIL-mediated CSR is important for humoral responses to T-cell-independent antigens.

Cytokines Involved in IgE Regulation

The second signal is mediated by cytokines secreted by the T cells. Th2 cells secreting IL-4 and IL-13 are the main inducers of IgE CSR. Through binding to their receptors, IL-4 and IL-13 mediate STAT6 phosphorylation. Activated STAT6 can bind to the Iε promoter and induce germline transcription at the Cε locus. Besides STAT6, which is the key regulator of ε-germline expression, there are several other factors needed for effective ε-germline transcription. These include NFκB, B-cell-specific activator protein (BSAP), C/EBP, and PU.1 (Delphin and Stavnezer 1995; Thienes et al. 1997). Both NFκB and PU.1 have a synergistic effect on STAT6-mediated activation of the Iε promoter. ε-germline transcription is initiated through a promoter located 5′ of the Iε exon upstream of the Cε exons. B cell lymphoma 6 (BCL-6) can inhibit Stat6-induced Iε transcription. The germline transcripts (GLT) are sterile transcripts because the I region contains stop codons within its reading frame preventing translation of the transcripts (Gauchat et al. 1990). IL-9 may also play a role in the induction of IgE expression. IL-9 activates STAT3 and STAT5 signaling, and it has a synergistic effect on IL-4-mediated IgE induction in germinal center B cells. IL-9 alone however does not induce IgE production (Fawaz et al. 2007).

Cross-References

- ▶ Diagnostic Components: T Helper Cell Cytokines (IL-4, IL-5, IL-9, IL-10, IL-13, IL-17)
- ▶ IgE Isotype Switching

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I

Insect Allergy in Children

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Synonyms

Anaphylaxis; Hymenoptera allergy; Hymenoptera hypersensitivity; Insect allergy; Insect hypersensitivity; Systemic allergic reaction

Definition

Insect allergy is a severe, IgE-mediated, life-threatening reaction to a stinging Hymenoptera.

The life-threatening allergic condition anaphylaxis has three common triggers: food, medication, and venom from stinging insects. All three of these anaphylactic triggers are the sources of considerable morbidity and mortality in children, but only insect allergy is treatable through means other than trigger avoidance. In the United States, potentially life-threatening systemic anaphylactic reactions may occur in 0.4–0.8 % of children, compared to adults, which see rates up to 3 %. Proper evaluation

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and treatment can make insect allergy nearly curable, with venom immunotherapy providing up to a 98 % level of protection from future insect-related anaphylactic events (Valentine et al. 1990; Golden et al. 2011).

Insect Terminology and Identification

Insects belonging to the order Hymenoptera account for the majority of serious sting-related reactions, both in adults and children. In North America, there are three families of Hymenoptera that are medically relevant: Apidae, Vespidae, and Formicidae. The family Vespidae includes the genera *Vespula* (yellow jacket), *Dolichovespula* (white-faced hornet and yellow hornet), and *Polistes* (paper wasp). The family Apidae includes the genera *Apis* (honeybee) and *Bombus* (bumblebee). The family Formicidae includes the genus S*olenopsis* (imported fire ant) (Freeman 2004; Muller et al. 2008; Golden 2009). Although there are other medically relevant stinging, biting, and venomous insects and arthropods, they are more extensively reviewed elsewhere and will not be the focus of this work (Demain 2003).

Knowledge of the biology, habits, and dwellings of these common culprits can aid in identifying the source of the sting and is helpful for the diagnosis and treatment of insect allergy. Identification is particularly helpful in children where avoidance education is the primary treatment option (Table 1).

Diagnosis

Hymenoptera stings in children often occur outdoors and during play. For instance, though honeybees are usually nonaggressive, children often suffer accidental stings by inadvertently stepping on them in the grass while barefoot. Imported fire ants (*Formicidae*) are ground dwelling and also play significant role insect allergy, especially young children during outdoor play and activities. Usually, children with venom allergy are non-atopic and atopic conditions such as food allergy are not considered risk factors (Novembre et al. 1998). Unlike in adults,

Insect Allergy in Children, Table 1 Hymenoptera biology and habitat

Common names	Taxonomic classification	Nesting habits	Feeding habit	Avoidance strategies
Honeybee[a]	Family Apidae	Commercial hives	Herbivorous. Nectar and pollen of flowering trees and plants	Avoid dark or flower-print clothing and wearing floral scents; wear shoes and socks
Yellow jacket	Family Vespidae Vespula species	Multilayered, usually underground; although there is also an aerial yellow jacket: Dolichovespula arenaria[b]	Scavengers, aggressive. Carnivorous	Avoid open food sources, picnic areas, garbage; destroy in-ground nests
Paper wasp[c]	Family Vespidae Polistes species	Hangs from eaves and porches	Nectar and arthropods	Avoid flower-print clothing and wearing floral scents; remove nests when possible
White-faced hornet	Family Vespidae Dolichovespula species	Multilayered, open areas	Nectar and arthropods	Avoid flower-print clothing and wearing floral scents; remove nests when possible
Fire ant	Family Formicidae	Earthen mounds in Southern United States	Omnivorous	Avoid mounds; wear shoes, sock and gloves

[a]A subspecies of honeybee exists in South Texas and Central and South America called "Africanized." It is more aggressive than local species and is clinically relevant in regions of infestation
[b]European species include *P. dominulus*, *P. gallicus*, and *P. nimphus*
[c]Paper wasps are not seen in the United Kingdom

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the culpable insect may not be apparent in children, but every effort should be made to identify the source of the sting.

In children, as in adults once the source of the reaction is identified, the diagnosis of Hymenoptera allergy is based upon a comprehensive clinical history, looking specifically at the presence of a systemic allergic symptoms and evidence of venom-specific IgE antibodies. If both criteria are met, then the child may be a candidate for venom immunotherapy.

Systemic allergic symptoms are rare. In most cases, the sting reaction is limited to self-limited local pain, tenderness, and swelling surrounding the sting site. Local reactions are defined as reactions that are confined to surrounding tissues and most resolve with local supportive treatment in 48–72 h. In 5–15 % of stings, a large local reaction, defined as a localized swelling of between 5 and 8 cm, can occur. When a systemic reaction occurs in children, approximately 60 % of cases are mild (Chipps et al. 1980). However, systemic allergic reactions are a critical component toward establishing the diagnosis of venom allergy. Systemic reactions can be mild and symptoms include minimal local flushing, urticaria, or angioedema. More serious symptoms in children can include bronchospasm, hypotension, and laryngeal edema manifesting as stridor. Children also have a better prognosis to re-sting event by both field stings and sting challenges when compared to adults. Nevertheless, fatal systemic reactions occur in 0.4–0.8 % of children compared to approximately 3 % of adults.

Management of Sting Reactions

Acute Management

Systemic reactions for anaphylaxis triggered by insect venom are managed the same as anaphylaxis caused by any other source, such as food or medication (Lieberman et al. 2011). The initial treatment of choice is intramuscular injection of epinephrine, preferably in the anterolateral thigh. An injection in the lateral thigh may achieve more rapid and higher plasma concentration than subcutaneous or intramuscular injection in the arm. The recommended dose is 0.01 mg/kg in children (up to 0.3 mg). Medications, such as oral or intravenous corticosteroids or histamine receptor blockers, are secondary medications that do not substitute for epinephrine. Patients allergic to insect venom should carry appropriate doses of autoinjectable epinephrine and be instructed as to its proper use.

Children who have had a suspected systemic reaction from an insect sting should be referred to allergist/immunologist experienced in the management of insect allergy. Children with a history of a suspected systemic reaction may be candidates for venom-specific IgE testing and venom immunotherapy. Other considerations include education regarding:

1. Risk of future sting events
2. Options for emergency and preventative treatment
3. Insect avoidance measures
4. Request consultation for additional information or venom-specific testing
5. Special counseling regarding protective value of approximately 98 % with venom immunotherapy

Evaluation for Venom-Specific IgE

Children with a systemic reaction to a Hymenoptera sting should be tested for venom-specific IgE. Venom-specific testing and venom immunotherapy is generally not necessary in children 16 years of age and younger who have experienced cutaneous systemic reactions such as urticaria without other systemic manifestations after an insect sting (Golden et al. 2004).

When testing for venom-specific IgE, skin testing is preferred over in vitro methods for initial tests because skin testing is more sensitive of approximately 80 % and is usually less costly. Skin test is most commonly performed using a combination of epicutaneous (prick/puncture) and intracutaneous (intradermal) methods accompanied by appropriate positive and negative controls. The technical specifics of venom skin testing are described in detail elsewhere (Golden et al. 2011; Krishna et al. 2011).

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Occasionally, false-positive and false-negative reactions may occur. False-positive reactions are usually caused by the inherent nonspecific irritant effect of the venom, usually at concentrations above 1 mcg/ml. False-negative reactions may be the result of reduced sensitivity to venom testing in the first few weeks after a systemic sting reaction may occur. As a result, venom testing should be deferred for 4–6 weeks so as to decrease the potential of a false-negative reaction.

Once skin testing is accomplished, a negative result with a significant history of a systemic allergic reaction should be interpreted with caution as skin testing can still up to 20 % of allergic individuals. Consequently, in vitro testing should be done in all patients with negative skin test responses who have a history of a systemic allergic reaction and who would be potential candidates for venom immunotherapy. The combination of venom skin testing and complementary in vitro testing detects 98 % of sensitized individuals (Golden et al. 2011). Dialyzed venom skin test preparations and recombinant in vitro products are not commercially available in the United States, but may be more sensitive in detecting venom sensitivity in such patients (Hamilton 2004). Baseline serum tryptase should be assessed, especially with negative venom-specific testing levels particularly in patients who had severe anaphylactic shock reactions to insect stings. Finally, especially in children, the stinging insect often cannot be reliably identified. Therefore, testing for all potentially relevant sensitivities requires testing with all of the commercially available bee and vespid venoms and may include testing to imported fire ants when the patient has potential regional exposure to fire ant stings.

Immunotherapy Indications for Large Local Reactions

Large local reactions are often caused by an IgE-mediated late-phase response and are generally not considered to be life threatening. In adults and children, large local reactions carry no more than a 5–10 % risk of a future systemic allergic reaction and testing is generally not indicated (Schuberth et al. 1982; Novembre et al. 1998). However, there are data to suggest that in some patients where the reactions are debilitating, or progressively worsening, many consider and benefit from venom immunotherapy (Graft et al. 1984; Golden et al. 2009). In these cases, venom testing may be indicated. The potential role for sublingual immunotherapy for large local reaction has also been investigated but remains investigational (Severino et al. 2008).

Venom Immunotherapy Protocols

In children 16 years of age and older where a sting event resulted in a systemic reaction, symptoms other than urticaria and angioedema, and evidence by skin test or in vitro methods of venom-specific IgE antibodies, that child should be referred to an allergy specialist and venom immunotherapy should be considered. Venom immunotherapy consists of gradually increasing doses of venom, usually beginning at 0.1–1.0 mcg/ml until a total dose of 100 mcg/ml is achieved for each of the venoms being treated. The usual venom load from a field sting for most Hymenoptera is 20–50 mcg/ml; therefore, a treatment dose of 100 mcg for each venom would represent a protective dose equivalent to between two and five field stings (Golden et al. 2011; Muller et al. 2008). The dose of 100 mcg per venom was established based on published protocols and is the manufactures' recommended dosing per the FDA-approved package inserts. An examination of the protective effect of venom immunotherapy in children has shown that a significant reduction in venom-specific IgE antibodies occurs over time, suggesting an inhibitory effect of venom-specific immunotherapy.

Imported fire ants (*S. invicta*) are ground-dwelling insects and present special challenges to children residing in fire ant endemic regions.

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Most physicians generally apply the same criteria in selecting patients to receive immunotherapy for fire ant allergy as other Hymenoptera allergy. However, unlike the other Hymenoptera, research has not established that children with only systemic cutaneous reactions are at risk or not for serious systemic reactions to subsequent sting. As there is a high risk of fire ant stings in children who live in areas in which fire ants are prevalent, immunotherapy can be considered for such children (Golden et al. 2011).

Duration of Venom Immunotherapy

While the majority of patients are sufficiently protected after completing a 5-year treatment plan, the optimal duration remains unclear (Graft et al. 1998). Indeed, an important number of children may never outgrow allergic reactions to Hymenoptera stings (Golden et al. 2004). As a result, in some cases, authors suggest that a lifetime of therapy may be warranted. Although some experts suggest that repeated venom skin testing can be helpful, the loss of skin test reactivity is not a guarantee of the loss of venom-induced anaphylaxis.

When evaluating whether to administer lifelong immunotherapy, it is important to note that children, as in adults, who have had experienced a previous life-threatening reactions are at greatest risk for similar life-threatening reactions after subsequent stings. In children with venom-specific sensitivity, venom immunotherapy can reduce the frequency and severity of future systemic reaction in patients with a previous history of moderate to severe systemic reactions to sting events. Other considerations for lifelong venom immunotherapy include whether the patient has a honeybee allergy or has had a systemic reaction and whether the patient requires a higher than usual venom dose, has severe anxiety over future stings, or has mast cell disease. Overall, venom immunotherapy therapy results in a significantly lower risk of systemic reactions to sting even 10–20 years after discontinuing treatment, with long-term benefit for children possibly exceeding than that seen in adults (Golden et al. 2004 and Gruchalla 2004).

Conclusion

Insect hypersensitivity is a source of considerable morbidity and mortality in children. However, unlike other common triggers of severe allergic reactions including foods and drug, insect hypersensitivity in children, as in adults, is nearly entirely curable. Proper education regarding insect biology and avoidance is especially important in children. However, when avoidance is neither practical nor possible and the systemic reaction is severe, venom immunotherapy should be offered. Proper evaluation is critical and when indicated, treatment with venom-specific immunotherapy a 98 % level of protection from future allergic sting reactions. The greatest single difference between children and adults with stinging insect allergy is the indication for venom-specific immunotherapy.

Cross-References

- Honeybee Allergy
- IgE Testing
- Immunotherapy, Mechanisms
- Imported Fire Ant Allergy
- Mastocytosis
- Methods (In Vivo): Skin Test (Intradermal, Puncture)
- Venom Content
- Vespid Allergy: Yellow Jackets, Hornets and Wasps

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Intranasal Anticholinergics

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Synonyms

Anticholinergic nasal spray; Intranasal antimuscarinics

Definition

Intranasal anticholinergics are approved for the treatment of rhinitis, commonly characterized by having one of the following nasal symptoms: rhinorrhea, congestion, sneezing, and nasal itching (Wallace et al. 2008). Other reported symptoms include throat clearing, headaches, facial pain, ear pain, itchy throat and palate, snoring, and sleep disturbances (Tran et al. 2011). They improve the symptoms of rhinitis by inhibiting serous and seromucous gland secretions locally (Atrovent® Nasal Spray package insert 2011). The only intranasal anticholinergic approved by the FDA is ipratropium bromide, marketed under the brand name Atrovent® Nasal Spray. Atrovent® Nasal Spray is approved for the symptomatic relief of rhinorrhea associated with the common cold or seasonal allergic rhinitis for adults and children aged 5 years and older. It does not have an effect on congestion or sneezing associated with the common cold or seasonal allergic rhinitis.

History

Antihistamines have been the cornerstone in the treatment of rhinitis and nasal mucosal

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inflammation; however, additional agents have been introduced to aid in the treatment of these conditions, including glucocorticosteroids, decongestants, and anticholinergics. The intranasal anticholinergic, ipratropium bromide, was derived from the anticholinergic atropine, which historically originates from the *Atropa belladonna* plant (Wood et al. 1995). Considerable interest in discovering anticholinergic agents began several decades ago, with increased understanding of the pathologies of the cholinergic nervous system (Wood et al. 1995). Concurrently, antihistamines have considerable anticholinergic properties (Scuderi 2003).

Mechanism of Action

Anticholinergics can ameliorate the symptoms of rhinitis, in particular rhinorrhea, by direct interference with the muscarinic receptors in the parasympathetic nervous system. Muscarinic receptors are G protein-coupled receptors (GPCR) and can be inhibitory or excitatory. Five subtypes of muscarinic receptors (M_1 through M_5) have been identified. Ipratropium nonselectively blocks all subtypes of muscarinic receptors (Scarpero and Dmochowski 2003). Intranasal administration of ipratropium causes parasympathetic stimulation in the nasal mucosa, resulting in reduced hypersecretion of the mucosal glands relieving rhinorrhea (Borts and Druce 1992). Increased parasympathetic stimulation leads to the release of muscarinic agonists, which stimulate muscarinic acetylcholine receptors and lead to increases in glandular secretion, vasodilation, and sinusoidal swelling.

Efficacy

The Joint Task Force on Practice Parameters states that the intranasal anticholinergic ipratropium bromide is effective in treating rhinorrhea in allergic rhinitis, nonallergic rhinitis, and the common cold (Wallace et al. 2008). It can be administered as monotherapy for rhinorrhea of nonallergic rhinitis syndromes and may have a special role in gustatory rhinitis. Although rhinorrhea symptoms are reduced, it does not affect other symptoms from seasonal or perennial allergic rhinitis. Concomitant use with intranasal corticosteroids or antihistamines has an additive effect in controlling rhinorrhea and is more effective than the administration of either one alone in treating rhinorrhea with limited increase in adverse effects (Wallace et al. 2008). Ipratropium bromide is generally not expected to treat nasal congestion (Wallace et al. 2008); however, there is limited evidence showing some benefit in controlling nasal congestion in children (Milgrom et al. 1999). In comparison to antihistamines, ipratropium bromide has been shown to be more effective at controlling parasympathetic causes of rhinitis compared to antihistamines in the absence of allergen-induced histamine release (Dykewicz et al. 1998).

Dosing

Ipratropium bromide, brand name Atrovent® Nasal Spray, is available as an isotonic aqueous solution at two concentrations, 0.03 % and 0.06 %. Ipratropium bromide 0.03 % is approved for the treatment of rhinorrhea with allergic and nonallergic perennial rhinitis in adults and children aged five and older. Ipratropium bromide 0.06 % is approved for the symptomatic relief of rhinorrhea associated with the common cold or seasonal allergic rhinitis for adults and children aged 5 years and older. See Table 1 for available indications, concentrations, and doses.

It is effective within minutes after application for persistent rhinorrhea. Ipratropium bromide has an average duration of action of 4–8 h.

Pharmacokinetics

Ipratropium bromide is a synthetic quaternary ammonium congener of atropine. The quaternary ammonium structure begets an ionized moiety on the molecule which results in low systemic

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Intranasal Anticholinergics, Table 1 Ipratropium bromide (Atrovent®) nasal spray: indications, concentrations, and doses (Atrovent®Nasal Spray package insert 2011)

Indication	Concentration (%)	Dose
Symptomatic relief of allergic and nonallergic rhinitis	0.03	Two sprays per nostril two to three times per day
The treatment of seasonal allergic rhinitis	0.06	Two sprays in each nostril four times per day
Symptomatic relief of rhinorrhea for the common cold	0.06	Two sprays in each nostril three to four times per day

absorption and does not readily cross the blood–brain barrier. As a result of the ionic property, less than 10 % of the intranasal dose is absorbed into circulation. This enables ipratropium to exert its effect primarily on the nasal mucosa (Wood et al. 1995; Dykewicz et al. 1998; Simasek and Blandino 2007). Ninety percent of the inhaled drug is swallowed, and the fraction that is absorbed is rapidly metabolized by ester hydrolysis and cleared by the kidneys (Borts and Druce 1992; Wood et al. 1995) with a half-life of 1.6 h. Ipratropium is less than 10 % protein bound (Wood et al. 1995).

Adverse Effects

Multiple studies of ipratropium bromide demonstrate tolerability, without evidence of rebound or mucosal damage and limited systemic adverse effects. The limited systemic adverse effects are due, in part, to the decreased systemic absorption.

Less than 2 % of patients report dry mouth/throat, dizziness, ocular irritation, blurred vision, conjunctivitis, hoarseness, cough, and taste perversion when taking ipratropium (Mandhane et al. 2011). Epistaxis and nasal dryness have been reported in 9 % and 5 % of patients, respectively (Wallace et al. 2008). No evident adverse psychological effects, alterations in sense of smell, ciliary beat frequency, and mucociliary clearance are observed with ipratropium bromide administration.

Summary

Ipratropium bromide nasal spray is an effective topical anticholinergic in the treatment of rhinorrhea in allergic rhinitis, nonallergic rhinitis, and the common cold. Ipratropium bromide is generally well tolerated. Atrovent® Nasal Spray is the only intranasal anticholinergic available. Concomitant use with intranasal corticosteroids or antihistamines results in additive properties for controlling rhinorrhea. Intranasal anticholinergics provide viable option for treating rhinitis because of their low incidence of side effects, including systemic anticholinergic activity (Wallace et al. 2008).

Cross-References

- ▶ Intranasal Antihistamines
- ▶ Intranasal Corticosteroids
- ▶ Intranasal Decongestants
- ▶ Intranasal Mast Cell Stabilizers

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Intranasal Antihistamines

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Synonyms

Histamine antagonists; Histamine blockers; Intranasal H_1 histamine antagonists; Intranasal H_1 histamine blockers; Topical antihistamines; Topical histamine antagonists; Topical histamine blockers

Definition

Antihistamines are a primary treatment of allergic rhinitis and have been associated with improved quality of life (Dykewicz et al. 1998). Allergic rhinitis is a common disorder and can have a profound effect on normal daily functions including fatigue, depression, and missed days of work and/or school and may affect learning. While systemic antihistamines have been in use for more than 60 years, intranasal antihistamines have become a popular option due to local application with decreased systemic adverse effects (Kaliner et al. 2011). Because many allergic rhinitis symptoms occur in the upper respiratory tract and sinus cavities, antihistamines delivered topically are a viable option for patients.

Mechanism of Action

Histamine is an autocoid amine synthesized from the decarboxylation of the essential amino acid, histidine. Histamine has multiple roles in the human body and is a common cause of many allergic symptoms. Allergens, with the aid of T-helper lymphocytes, stimulate B-lymphocytes. B-lymophocytes release IgE antibodies, which bind to the high affinity IgE receptor (FcεRI) on mast cells and basophils. Further exposure to the allergen cross-links the IgE and FcεRI and causes degranulation and release of histamine from the mast cells and basophils. Histamine type 1 (H_1) receptors are found in dermal tissue, smooth muscle, vascular epithelium, and airway epithelium.

The inflammatory response is initiated with H_1 receptors binding histamine and subsequently activates second messenger systems, phospholipase C, inositol phosphate, and diacylglycerol production, and thus increases calcium release from endoplasmic reticulum stores (Thurmond et al. 2008; Nijmeijer et al. 2010). This results in vasodilation, increased vascular permeability, and the release of inflammatory markers such as cytokines, prostaglandins, cytokines, and nitric oxide (Nijmeijer et al. 2010).

H_1 antagonists (antihistamines) reversibly and competitively bind H_1 receptors and act as inverse agonists. This decreases histamine's ability to H_1 receptors thus attenuating the physiological effect of histamine associated with the symptoms of allergic rhinitis such as rhinorrhea.

To date, there are two FDA-approved intranasal antihistamines. Azelastine hydrochloride, a phthalazinone derivative, was the first intranasal antihistamine approved for use in the United States in 1996 (Dykewicz et al. 1998). There are two available products that contain azelastine: Astelin® and Astepro®. Both are indicated for seasonal allergic rhinitis treatment but have

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Intranasal Antihistamines, Table 1 Intranasal antihistamines dosing information. The onset of action for these agents is 15 min (Astelin® 2006; Astepro® 2013; Patanase® 2012)

Intranasal antihistamine	Brand name	General dosing recommendations
Azelastine hydrochloride	Astelin® 0.1 %	Astelin®:
		Seasonal allergic rhinitis – patients ≥ 12 years: 1–2 sprays (137 mcg/spray) per nostril twice daily
		Vasomotor rhinitis – patients ≥ 12 years: 2 sprays per nostril twice daily
Azelastine hydrochloride	Astepro® 0.1 %, 0.15 %	Astepro®:
		Seasonal allergic rhinitis – 1–2 sprays (205.5 mcg/spray) per nostril twice daily or 2 sprays per nostril once daily
		Age 6–11: 1 spray per nostril twice daily (Astelin® or Astepro®)
Olopatadine hydrochloride	Patanase®	Seasonal allergic rhinitis – 2 sprays in each nostril twice a day
		Age 6–11: 1 spray in each nostril twice daily
		Patients < 6 years old have not been studied

different age indications (Table 1). Astelin® is also approved for treatment of nonallergic vasomotor rhinitis. Because of the objectionable bitter taste of Astelin®, Astepro® was originally developed to alter the formulation to include sorbitol and sucralose. Azelastine is a potent H_1 receptor antagonist with minimal anticholinergic activity. In preclinical and clinical studies, azelastine inhibited the synthesis and release of immunomodulatory markers including leukotrienes and antagonized the effects of histamine, acetylcholine, serotonin, and bradykinin.

Olopatadine hydrochloride, Patanase®, was introduced to the US market in 2008 and is approved for seasonal allergic rhinitis. Olopatadine is a mast cell stabilizer (thereby inhibiting the release of histamine) and a selective H_1 receptor antagonist and decreases chemotaxis and activation of eosinophils. In preclinical studies, olopatadine hydrochloride was observed to inhibit inflammatory markers such as platelet-activating factor (PAF), immunoglobulin E (IgE), and leukotriene B4 (LTB_4) (Meltzer et al. 2005).

Efficacy

In assessing efficacy, randomized clinical trials will utilize Total Nasal Symptom Score (TNSS) or modified versions of this scale which is a subjective patient assessment of their symptoms of rhinorrhea, nasal congestion, nasal itching, and sneezing with the total scores ranging from 0 to 9 points with each domain given a score ranging from 0 to 3 points with a score of 0 equating to no symptoms and a score of 3 classified as severe. According to a joint task force for the diagnosis and management of rhinitis, intranasal antihistamines may be considered as first-line agents in the treatment of allergic rhinitis (Wallace et al. 2008). Randomized controlled trials have demonstrated azelastine and olopatadine to be more effective than placebo in the management of symptoms associated with allergic rhinitis (Lumry et al. 2007; Meltzer et al. 2005).

In a double-blind, randomized placebo-controlled trial, 554 patients with seasonal allergic rhinitis were treated with either azelastine or placebo for 2 weeks. Azelastine showed greater TNSS improvement compared to placebo with an average 2.69 increase in azelastine-treated group compared to 1.31 increase in the placebo ($p = 0.01$) (Lumry 2007). Similarly, in a double-blind randomized controlled trial, 565 patients with season allergic rhinitis were treated with either olopatadine or placebo for 2 weeks. Olopatadine showed greater reduction in average percent reductions in Reflective Total Nasal Symptom Score, 39.2 % reduction, compared to placebo, 27 % reduction ($p < 0.001$) (Meltzer et al. 2005).

Azelastine and olopatadine were evaluated for efficacy and tolerability in a phase 3, multicenter, randomized, double-blind placebo-controlled parallel group trial measuring TNSS. Azelastine and olopatadine resulted in similar reductions in TNSS of 26.8 % and 29.9 % (95 % CI, −2.5 % to 8.7 %)

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and both resulted in greater reduction in TNSS compared to placebo (18.4 %, $p = 0.003$ for olopatadine compared to placebo, the p-value for azelastine was not reported) (Shah et al. 2009).

Pharmacokinetics

Azelastine Hydrochloride

After intranasal administration, azelastine hydrochloride has a systemic bioavailability of about 40 %. Maximum serum concentrations (C_{max}) are systemically achieved in 2–3 h. Studies based on oral administration found azelastine is excreted approximately 75 % in feces and less than 10 % excreted unchanged in urine. Approximate elimination half-life is 22 h, steady state volume of distribution is 14.5 L/kg, and plasma clearance is 0.5 L/h/kg. Cytochrome P450 2D6 is the primary metabolic enzyme responsible for the biotransformation of azelastine, and desmethylazelastine is the major active metabolite (Imai et al. 1999; Nakajima et al. 1999). General dosing recommendations and selected pharmacokinetic parameters are listed in Table 1.

Olopatadine Hydrochloride

Olopatadine pharmacokinetic properties have been studied with nasal, oral, intravenous, and topical ocular administration. Olopatadine exhibits linear pharmacokinetics. The average absolute bioavailability of intranasal olopatadine is 57 %, with C_{max} from 15 min and 2 h. Olopatadine is mainly excreted in the urine with a serum half-life of 8–12 h. Protein binding is 55 %. Olopatadine has at least six metabolites that have been found (including the mono-desmethyl and *N*-oxide). General dosing recommendations and selected pharmacokinetic parameters are listed in Table 1 (Ohmori et al. 2002).

Safety

Intranasal antihistamines are generally well tolerated because of their low systemic absorption. In a 4-week multicenter comparative trial of 264 subjects 12 years of age and older, altered taste was the most commonly occurring adverse event reported with azelastine use (30 % with 2 sprays per nostril twice daily). Although transient and brief in duration, altered taste was statistically significantly different from placebo. Other adverse events included mild, self-limiting epistaxis, transient burning sensations, and local irritation at site of administration (LaForce 1996). A 2-week, randomized, placebo-controlled group trial in patients with moderate to severe seasonal allergic rhinitis observed similar results with the exception of bitter taste, with a prevalence of 8.3 % (Lumry et al. 2007). Other adverse events reported include somnolence (0.9–2 %), headache (1–4 %), nasal discomfort (1–4 %), and epistaxis (2–6 %) (Astepro® prescribing information 2013).

Similar safety profile has been observed with olopatadine hydrochloride. Olopatadine safety was evaluated in three randomized, double-blind, parallel group multicenter placebo-controlled clinical trials of 1,180 patients 12 years and older with seasonal allergic rhinitis. These studies were conducted over 2 weeks, and the adverse reactions that were observed more often than placebo group included bitter taste (12.8 % vs. 0.8 %), headache (4.4 % vs. 4.0 %), epistaxis (3.2 % vs. 1.7 %), and pharyngolaryngeal pain (2.2 % vs. 1.3 %) (Ohmori et al. 2002).

Azelastine nasal spray has been reported to cause somnolence (Lumry 2007). CNS depressants or alcohol is recommended to be avoided because additional reductions in alertness and impairment may occur. Olopatadine interactions with liver enzyme inhibitors are not a concern secondary to its predominant renal excretion. Due to modest protein binding (55 %) of olopatadine, drug interactions through displacement are also not a concern (Lumry et al. 2007; Ohmori et al. 2002).

Intranasal Versus Oral Antihistamines

Intranasal and oral antihistamines are first-line treatments for allergic rhinitis. Intranasal antihistamines are applied topically and locally to bind to H_1 receptors in the target nasal mucosa tissue that

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is inflamed due to the action of histamine. Topical application has the advantage of a more rapid onset of action and lower systemic absorption. The consequence of a lower systemic absorption is a decreased incidence of adverse effects compared to oral antihistamines. Intranasal antihistamines are associated with clinically significant treatment of nasal congestion. Because of these differences, intranasal agents may be preferred in patients with nasal congestion as the major symptom. Oral antihistamines would also be recommended for patients with medication adherence problems and children. Oral antihistamines are approved in younger children, up to 2 years and up (Chipps and Harder 2009).

Conclusion

Intranasal antihistamines play a crucial role in mitigating the inflammatory process associated with rhinitis and are a favorable treatment option in patients with allergic rhinitis. Topical application has the advantage of a more rapid onset of action and lower systemic adverse effects (with the caveat of somnolence being reported in the use of azelastine). They are considered first-line agents in the treatment of allergic rhinitis and can have effects on nasal congestion (Wallace et al. 2008).

Cross-References

- Intranasal Anticholinergics
- Intranasal Corticosteroids
- Intranasal Decongestants
- Intranasal Mast Cell Stabilizers
- Ocular Antihistamines
- Oral Antihistamines
- Topical Antihistamines

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Intranasal Corticosteroids

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Synonyms

Nasal corticosteroid; Nasal glucocorticoid; Nasal steroid

Definition

Allergic rhinitis (AR) is an immune-mediated response to indoor and outdoor allergens. It is characterized by symptoms including rhinorrhea, nasal congestion, and pruritus (Sur and Scandale 2010). Intranasal corticosteroids (INCS) are the cornerstone of pharmacotherapy for both seasonal (SAR) and perennial allergic rhinitis (PAR) (Derendorf and Meltzer 2008) (Szefler 2001). Other therapeutic indications for INCS include chronic rhinosinusitis, rhinitis medicamentosa, and non-allergic rhinitis (Szefler 2001).

Mechanism of Action

Intranasal corticosteroids have the advantage of topical and local administration to the nasal mucosa. Mechanistically, the glucocorticoid (GC) binds to the glucocorticoid receptor (GR) complex (with several heat shock proteins, and other proteins), located within the cytoplasm of the target cell (Adcock and Caramori 2001). The bound GC-GR complex is then translocated to the nucleus and in the nucleus, and interacts with GC responsive elements, subsequently altering gene transcription of certain key mediators in the inflammatory process (e.g., interleukins, chemokines, and phospholipase A_2) (Barnes et al. 1998).

Drug Information

Please refer to Table 1, Drug information for intranasal corticosteroids for allergic rhinitis, for a summary of generic and brand names, strengths available, and dosing.

Pharmacokinetics

Lipophilicity dictates the ability of INCS to be absorbed through the nasal mucosa and the length of time in the nasal tissue to have an effect. The more lipophilic the corticosteroid, the longer it will be retained within the nasal tissue. Lipophilicity was compared among INCS in one study, and mometasone furoate was the most lipid-soluble followed by beclomethasone dipropionate, budesonide, triamcinolone, and flunisolide (Corren 1999). Additionally, ciclesonide was determined to be more lipophilic than fluticasone propionate (Miller-Larsson et al. 2003). As lipophilicity of a drug increases, the volume of distribution (Vd) generally increases as well. Another determinate of Vd is plasma protein binding. Once the INCS are absorbed systemically, they are highly protein bound (e.g., beclomethasone dipropionate 87 %, budesonide 88 %, fluticasone propionate 90 %, and triamcinolone acetonide 71 %) (Derendorf et al. 1998). Examples of various Vd from intravenous administration are 1.9 L/kg for triamcinolone, 1.8 L/kg for flunisolide, and 2.7 L/kg for budesonide (Szefler 2001). Little is known about the metabolism of INCS in nasal tissue; however, a large portion of the drug administered nasally is swallowed and undergoes first-pass metabolism. Due to extensive metabolism, very little of the drug reaches systemic circulation (Derendorf and Meltzer 2008).

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Intranasal Corticosteroids, Table 1 Drug information for intranasal corticosteroids for allergic rhinitis

Drug name	Common brand name	Strength	Dosing in adults and children >12	Dosing in adolescents and children < 12
Beclomethasone dipropionate	Beconase AQ®	42 mcg/spray	One to two sprays per nostril twice daily (168–336 mcg/day)	*Children 6–12* One spray per nostril twice daily; may increase to Two sprays twice daily
Beclomethasone dipropionate	Qnasl®	80 mcg/spray	Two sprays in each nostril daily (320 mcg/day)	Not recommended
Budesonide	Rhinocort Aqua®	32 mcg/spray	Two sprays each nostril daily (max 256 mcg/day)	*Children 6–12* One spray each nostril daily (max 128 mcg/day)
Ciclesonide	Omnaris®	50 mcg/spray	Two sprays per nostril daily	Not recommended
Flunisolide	Nasarel®	25 mcg/spray	*Age ≥ 14* Two sprays per nostril twice daily may increase to Two sprays per nostril three times a day	*Age 6–14* One spray per nostril three times daily or two sprays per nostril twice daily
Fluticasone propionate	Flonase®	50 mcg/spray	Two sprays per nostril daily or one spray per nostril twice daily	*Children 4 and older* One spray in each nostril daily may increase to two sprays in each nostril daily
Fluticasone furonate	Veramyst®	27.5 mcg/spray	Two sprays per nostril once daily, may decrease to one spray per nostril daily when symptoms are controlled	*Children 2–12* One spray in each nostril once daily, may increase to two sprays in each nostril daily and reduce back to one spray per nostril when symptoms are controlled
Mometasone	Nasonex®	50 mcg/spray	Two sprays per nostril once daily	*Children 2–11* One spray per nostril daily
Triamcinolone acetonide	Nasacort AQ®	55 mcg/spray	Two sprays in each nostril once daily	*Children 2–5* One spray per nostril daily (max 110 mcg/day) *Children 6–12* One spray per nostril daily (max dose 220 mcg/day)

McEvoy (2006), Clinical Pharmacology Web site

Clinical Safety and Efficacy

Common side effects observed with INCS include epistaxis, hoarseness, nasal dryness, stinging, and irritation (Derendorf and Meltzer 2008). Oral corticosteroids have been linked with growth suppression in children and HPA axis suppression in both children and adults; however, because of the decreased systemic bioavailability with INCS, it is not clear. One trial by Skoner and colleagues investigated this effect in triamcinolone acetonide and fluticasone propionate in 49 participants with an average age of 7 years. The mean growth velocity of children using these products compared to placebo did not demonstrate a statistically significant difference. Additionally, no significant differences were noted in urine cortisol/creatinine ratios between triamcinolone acetonide and placebo. The change in urine cortisol/creatinine ratio was, however, significantly lower with intranasal fluticasone propionate compared to placebo (Skoner et al. 2003). No prior effects on the HPA axis were noted in previous studies involving adults and children using INCS (Boner 2001). Longer studies (1 year) evaluating in children using mometasone furoate, fluticasone propionate, and ciclesonide did not demonstrate growth

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suppression versus placebo (Schnekel et al. 2000; Allen et al. 2002; Skoner 2006).

Very few studies involving INCS focus on onset of action. It has generally been accepted that most patients will notice symptom improvement within days to weeks (Derendorf and Meltzer 2008). One study by Berkowitz et al. noted mometasone furoate can provide symptom relief as soon as 5 h in patients with seasonal allergic rhinitis (1999).

A meta-analysis was conducted for the efficacy of INCS and oral antihistamines in the treatment of allergic rhinitis (Weiner et al. 1998). Based on a review of the literature, there is no one INCS that is superior to another in controlling symptoms of perennial and seasonal allergies, decreasing costs and adverse effects (Waddell et al. 2003). At the time of the meta-analysis, several INCS, such as ciclesonide, and fluticasone furoate/propionate, were not on the market. Further studies are needed to determine superiority of one agent; however, many of the INCS have different age restrictions, making options limited for certain patients.

Cervin and Anderson identified 11 case reports of septum perforation from their clinic over 5 years attributable to INCS. Thirty-eight cases were also identified from the Swedish Medical Products Agency database over a 10-year period, with 23 of the cases linked with Rhinocort Aqua (Cervin and Andersson 1998). The authors concluded that septal perforations are rarely discussed in literature and may be an overlooked complication (Cervin and Andersson 1998). Other adverse effects include allergic contact dermatitis, which has been shown to occur in few cases, specifically with budesonide usage (Bircher et al. 1996).

In October 2013, the US Food and Drug Administration approved triamcinolone acetonide nasal spray for over-the-counter (OTC) treatment of SAR and PAR for ages 2 and older. This is the first intranasal glucocorticoid approved for OTC in the US market. Eleven countries have already approved the use of this agent as a non-prescription medication. The FDA advisory committee voted 10 to 6 in July of 2013 in favor of making triamcinolone acetonide available as an OTC product, but safety concerns existed, specifically with growth suppression. Triamcinolone acetate should be made available in mid-2014, with a warrning label alerting of its potential adverse effect of a slower growth rate in childern. Additionally, a pediatrician should be consulted if a child is to administer this product for greater than 2 months within a 12 months period (Nonprescription Drug Advisory Committee 2013; FDA 2013).

Drug Interactions

Intranasal corticosteroids exhibit poor systemic bioavailability; therefore, occurrence of drug interactions is seldom. However, there have been case reports listed Cushing Syndrome and adrenal suppression as adverse effects with the concomitant use of fluticasone propionate and ritonavir, a cytochrome P450 3A4 inhibitor (Flonase Package insert). As a result, fluticasone propionate should be avoided in patients currently administering 3A4 inhibitors (e.g., fluconazole, ciprofloxacin, and clarithromycin) (Flonase Package insert).

Conclusion

Intranasal corticosteroids are the cornerstone of modern pharmacotherapy in the treatment of seasonal and perennial allergic rhinitis in adults and children (Scadding et al. 2008). When utilized properly, the specific medications among this class demonstrate comparable effectiveness. Differences among them are usually limited to dosing regimens, patient preferences, and the delivery device and tolerability of the vehicle. Nonetheless, newer agents, such as ciclesonide, fluticasone propionate, and fluticasone furoate, provide for once daily dosing, leading to compliance improvement. Concerns exist for INCS causing HPA axis suppression and growth suppression in children. Studies to date have been inconclusive and need to be evaluated in a larger patient sample to definitively rule out such vital safety risks.

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Cross-References

- ▶ Allergen Avoidance: Pollen Avoidance - Tree, Grass, and Weed
- ▶ Oral Corticosteroids

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Intranasal Decongestants

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Synonyms

Topical decongestants; Topical sympathomimetics; Topical vasoconstrictors

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Definition

Intranasal decongestants are widely used to provide relief of nasal congestion. There are multiple causes for nasal congestion, including allergic rhinitis, vasomotor rhinitis, chronic sinusitis, and viruses affecting the upper respiratory tract (Corey et al. 2000). Direct adrenergic agonists elicit a sympathetic response that induces vasoconstriction of the blood vessels in the nose which reduces swelling and gland secretion. Intranasal decongestants are primarily used to treat nasal congestion, and are not effective against rhinitis symptoms, including rhinorrhea, sneezing, and itching (Bousquet et al. 2008). Practice guidelines do not support intranasal decongestant use in bacterial rhinosinusitis, an infection where the nasal cavity and paranasal sinuses become inflamed (Chow et al. 2012). Because intranasal decongestants as a sole therapy are not appropriate for long-term use, the duration of therapy must be taken into account.

Mechanism of Action

Normally, blood vessels in the venous sinuses exist in a mixed state of dilation and constriction; this maintains local patency, allowing for free passage of air through the nasal cavity. An insult to the local airway (aforementioned by multiple causes) will induce vasodilation and hence swelling of the nasal and sinus tissue. This swelling can partially or completely obstruct the nasal passage. The venous sinuses are innervated by the sympathetic adrenergic neurons; thus, a constitutive sympathetic release is needed in order to keep the nasal blood vessels constricted (Eccles 2000). Norepinephrine was discovered to be the primary neurotransmitter of the nasal sympathetic system (Lacroix et al. 1989). Parasympathetic responses, in contrast, were found to have little effect on nasal blood volume – although it is thought to have more responsibility with rhinorrhea (Eccles 2000).

Sympathetic drugs cause vasoconstriction of the nasal blood vessels and decongestion of the nasal venous sinuses. These medications are categorized either as sympathomimetics amines (i.e., ephedrine and phenylephrine) or imidazoline derivatives (i.e., naphazoline, tetrahydrozoline, xylometazoline, and oxymetazoline). They imitate the effects of norepinephrine and epinephrine, and act on alpha-1 and alpha-2 receptors in the venous sinuses. Sympathomimetics amines target the alpha receptors, but also have mild agonist effects on beta receptors. Imidazoline derivatives mainly affect the alpha-2 receptors (Lockey 2006). These decongestants stimulate the sympathetic system and cause vasoconstriction of sinus blood vessels, reducing the volume displaced by the venous sinus tissue and, consequently, airflow resistance (Corey et al. 2000). The most commonly used topical decongestants and their formulations are provided in Table 1. Dosing information for both children and adults is contained in Table 2.

Clinical Trials

Nasal decongestants are used in the outpatient setting to measure nasal blockage reversibility. A poor response to nasal decongestants may suggest sinusitis. Nasal blockage reversibility due to topical decongestants can be a predictor of response to long-term use of intranasal corticosteroids for persistent allergic rhinitis (Barnes et al. 2005). Few clinical trials exist involving topical decongestants in the allergic rhinitis setting. A clinical trial involving 36 patients compared and correlated the effects of xylometazoline 0.1 % (one spray in each nostril) after 15 min with that of mometasone 200 mcg (one spray in each nostril) for 28 days. Effects of xylometazoline were measured on two separate occasions and then subjects underwent a randomized, double-blind cross-over period to placebo or mometasone for 28 days (Barnes et al. 2005). The investigators measured peak nasal inspiratory flow (PNIF), nasal flow inspiratory volume in 1 s ($nFIV_1$), and nasal blockage score (NBS). Data from this study demonstrated a median percent improvement in PNIF of 20 % (11.4–31, 95%CI) with xylometazoline and 9.6 %

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Intranasal Decongestants, Table 1 Drug information for common intranasal decongestants

Active ingredient	Common brand name (company)	Strength	Dosage form	Duration of action
Oxymetazoline hydrochloride	Afrin (Schering Plough)	0.05 %	Spray	Long acting
Phenylephrine	Vicks Sinex (Procter & Gamble)	0.25 %, 0.5 %, 1%	Spray	Short acting
Propylhexedrine	Benzedrex (B.F. Ascher)	0.4–0.5 mg	Inhalation	Short acting
Tetrahydrozoline chloride	Tyzine (Fougera Pharms)	0.1 %	Spray	Short acting
Xylometazoline	Otrivin (Novartis)	0.05 %, 0.1 %	Spray	Intermediate acting

Intranasal Decongestants, Table 2 Child and adult dosage information for common intranasal decongestants

Active ingredient	Adults and children > 12 years	Children 6–12 years	Children 2–6 years
Oxymetazoline hydrochloride	2–3 sprays/drops every 10–12 h	1–2 sprays every 10–12 h	Not recommended
Phenylephrine	2–3 sprays/drops every 4 h	Not recommended	Not recommended
Propylhexedrine	1–2 inhalations in each nostril every 2 h	1–2 inhalations in each nostril every 2 h	Not recommended
Tetrahydrzoline chloride	2–3 sprays every 4–6 h	2–3 sprays every 4–6 h	0.05 %: 2–3 sprays every 4–6 h
Xylometazoline	2–3 sprays every 8–10 h	Not recommended	Not recommended

(3.2–15.8, 95%CI) with mometasone. Median percent $nFIV_1$ with xylometazoline was also greater than mometasone 17.8 (10.0 to 28.1) versus 3.3 (−4.3 to 19.1), respectively. Data from this study did not demonstrate correlation with response to chronic use of mometasone after acute xylometazoline for PNIF ($r = 0.144$, $p = 0.431$), $nFIV_1$ ($r = 0.252$, $p = 0.165$) and NBS ($r = 0.294$, $p = 0.103$). The authors warned that while nasal decongestants relieve nasal blockage to a larger extent than corticosteroids in persistent allergic rhinitis, the potential for rhinitis medicamentosa is likely with long-term use. Additionally, intranasal corticosteroids also provide relief for inflammation, sneezing, itching, and nasal discharge, whereas nasal decongestants do not (Barnes et al. 2005).

In a larger, more recent phase 2 clinical trial, the effects of an intranasal decongestant were investigated when combined with an intranasal steroid. Study participants ≥ 12 years of age were randomized to one of five groups: mometasone furoate nasal spray of 200 mcg spray daily plus oxymetazoline 0.05 % 3 sprays per nostril once daily, mometasone furoate 200 mcg spray daily plus oxymetazoline 0.05 % 1 sprays per nostril once daily, mometasone furoate 200 mcg daily, oxymetazoline 0.05 % 1 sprays per nostril twice daily, or placebo for 15 days (Meltzer et al. 2013). The primary endpoints for this study were changes in baseline morning and evening instantaneous total nasal symptom scores (TNSS) from days 1 to 15 and AUC (0–4 h) changes from baseline in congestion on day 1. The combinations of oxymetazoline plus mometasone significantly reduced TNSS scores compared to placebo or oxymetazoline alone ($p \leq 0.002$). Additionally, AUC changes from baseline day 1 congestion were significantly improved with combination mometasone and oxymetazoline (−0.92 mometasone with 3 sprays per nostril once daily of oxymetazoline and −0.80 with mometasone with 1 spray/day of oxymetazoline) or oxymetazoline alone (−1.06) compared to mometasone alone (−0.63) or placebo (−0.57). The adverse effects were similar among the treatment groups. The authors concluded combining oxymetazoline with mometasone relieves symptoms faster than mometasone alone and with better efficacy that with oxymetazoline alone.

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Intranasal Decongestants, Table 3 Pharmacokinetics for common intranasal decongestants

Active ingredient	Absorption	Distribution	Metabolism	Excretion	Duration of action
Oxymetazoline hydrochloride	Rapid absorption in nasal mucosa; onset 5–10 min	Data not available in humans; high doses systemic distribution can occur	Unknown; Evidence of CYP2C19 metabolism in liver	Data not available in humans	5–6 h with gradual decline for another 6 h
Phenylephrine	Rapid absorption in nasal mucosa	Data not available in humans; high doses systemic distribution can occur	Metabolism occurs in liver and intestine by monoamine oxidase	80 % urine	3–4 h
Propylhexedrine	Rapid absorption in nasal mucosa; onset 30 s to 5 min	Data not available in humans; high doses systemic distribution can occur	Liver	Urine and excreted as norpropylhexedrine, cyclohexylacetoxine and 4-hydroxyproplhexedrine	Up to 2 h
Tetrahydrzoline chloride	Rapid absorption in nasal mucosa; onset occurs in minutes	Data not available in humans; high doses systemic distribution can occur	Unknown	Data not available in humans	4–8 h

Safety and Side Effects

Adverse effects of topical decongestants include nasal burning, stinging, dryness, mucosal ulcerations, and septal perforations (Mandhane et al. 2011). Systemic side effects are rare in topical formulations of decongestants and are less pronounced than oral formulations; these include hypertension, palpitations, restlessness, agitation, tremor, insomnia, headache, dry mucous membranes, urinary retention, and exacerbation of glaucoma or thyrotoxicosis (Bousquet et al. 2008) (Mandhane et al. 2011). Rhinitis medicamentosa, or rebound congestion, is characterized by symptoms of vasodilation and intravascular edema of nasal vasculature (Bousquet et al. 2008). The timing of rhinitis medicamentosa is poorly defined, but typically occurs within 3–10 days of repeated use of nasal decongestants (Ramey et al. 2006). The mechanism for rhinitis medicamentosa is not fully understood; however, it is thought that the decongestant-agonized alpha receptors undergo tachyphylaxis and are desensitized to the repeated stimulation after prolonged treatment, which results in greater congestion (Lockey 2006). If rhinitis medicamentosa should develop, decongestant treatment must be discontinued to allow the nasal mucosa to recover. Upon cessation of intranasal decongestant treatment, swelling and congestion likely worsen. To aid in relief, implementation of intranasal corticosteroids can be used to decrease edema, inflammation, and congestion (Lockey 2006). One successful method includes the administration of a short course of systemic corticosteroids with an intranasal steroid, while a taper of the intranasal decongestant (Lockey 2006).

Drug Interactions

CYP P4502C19 has been observed to be a primary enzyme in the metabolism of oxymetazoline (Mahajan et al. 2011); however, systemic absorption from topical nasal decongestants is poor, making drug interactions unlikely (Mandhane et al. 2011; Nathan 2008). The pharmacokinetics and metabolism of some selected intranasal decongestants are included in Table 3.

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Conclusion

Nasal congestion is commonly experienced in maladies including allergic rhinitis, vasomotor rhinitis, chronic sinusitis, and viral infections. Intranasal decongestants as a sole therapy are often utilized and have great short-term success in providing temporary relief from congestion. Rhinitis without congestion will not be relieved by intranasal decongestants. Because of the risk of rhinitis medicamentosa, patients should exercise caution in avoiding nasal decongestants for more than 3–5 days. Recently, a clinical trial has demonstrated significant benefit in combining an intranasal decongestant with an intranasal steroid.

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Intranasal Mast Cell Stabilizers

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Synonyms

Cromolyn sodium; Nasalcrom; Nedocromil; Sodium cromoglycate

Definition

Mast cell stabilizers are used for the prevention of seasonal and perennial allergic rhinitis. They prevent the mast cell release of performed mediators (e.g., histamine), newly formed lipid mediators (e.g., leukotrienes), and cytokines (e.g., eosinophil chemotactic factor) by inhibiting degranulation after contact with antigens (Pearce et al. 1989). Intranasal mast cell stabilizers are designed for direct application to the nasal mucosa and are useful in the prevention of allergic rhinitis. They have little effect on an existing episode of rhinitis (Sur and Scandale 2010). Cromolyn sodium (aka sodium cromoglycate) is currently the only intranasal mast cell stabilizer approved by the FDA for the treatment of seasonal allergic rhinitis and has been available since 1983. It is available over the counter as a dose of 5.2 mg/actuation.

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Mechanism of Action

Mast cell stabilizers block the function of chloride channels and prevent extracellular calcium influx into the cytoplasm of the mast cell, thereby preventing degranulation and the subsequent release of inflammatory mediators from mast cells (Mandhane et al. 2011). Histamine and leukotrienes cause a quick onset inflammatory response, while leukotrienes alone cause a delayed and sustained inflammatory response. By inhibiting the release of these mediators, mast cell stabilizers are able to prevent both the early and late phases of the allergic reaction (Mandhane et al. 2011). Mast cell stabilizers do not have an effect on vasomotor rhinitis, nonallergic rhinitis with eosinophilia, or nasal polyposis.

Pharmacokinetics

Cromolyn sodium exhibits poor systemic absorption when used intranasally. Once administered, cromolyn acts locally and less than 7 % of the medication is absorbed and excreted unchanged in bile and urine (Ratner et al. 2002).

Dosing

See Table 1 for dosing information for cromolyn sodium. Dosing is frequent, from three times up to six times per day. Patient adherence may be a barrier to ideal use and thereby limit the full clinical effect of intranasal cromolyn sodium. For allergic rhinitis prophylaxis, up to a full week of therapy may be needed prior to allergen exposure.

Clinical Trials

In a 1975 trial, a 4 % nebulized aqueous solution of cromolyn sodium was evaluated in a 9-week double-blind, placebo-controlled study of 104 patients with pollen-induced seasonal allergic rhinitis and showed reductions in mean daily scores of rhinorrhea ($p = 0.001$), nasal congestion ($p = 0.008$), and sneezing ($p = 0.013$) compared to placebo (Handelman et al. 1977).

Intranasal Mast Cell Stabilizers, Table 1 Dosing information for cromolyn sodium

FDA-approved indication	Allergic rhinitis
Dosage forms	Nasal spray – 5.2 mg/actuation
Dose recommendations	Allergic rhinitis: adults and children >2 years of age – one spray in each nostril three to four times per day, up to six times per day as needed
Dose adjustments	No dose adjustments are provided in manufacturer's labeling for renal or hepatic impairment

Cromolyn sodium was evaluated in a 2-week randomized, double-blind, placebo-controlled, intent-to-treat parallel-group design multicenter study of 1,150 patients (580 cromolyn, 570 placebo) with allergic rhinitis (Meltzer 2002). Participants were required to refrain from using OTC allergy medications within 48 h of the study entry. Patients rated symptom severity, symptom relief, medication efficacy, and helpfulness of the label instructions. Relief of individual rhinitis symptoms was assessed at the end of weeks one and two. Cromolyn provided greater relief than placebo on all efficacy measures and was statistically significantly more effective than placebo in controlling symptoms ($p = 0.02$), providing overall symptom relief ($p = 0.02$), and relieving sneezing ($p = 0.01$) and nasal congestion ($p = 0.03$). These improvements were seen with 48 % of patients not using the full number of recommended daily doses likely due to using the medication on an as-needed basis (Meltzer 2002). It can take between 1 and 2 weeks to see the full effect of cromolyn use; however, the study length of this trial was 2 weeks. Therefore, the full effects of this medication may have not been reached during this study period. No safety concerns with the use of cromolyn were noted in this trial.

Safety and Side Effects

Cromolyn is regarded as generally safe and is associated with few adverse effects. If seen, adverse effects include headaches, increased

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sneezing, burning, nasal irritation, unpleasant taste, and hoarseness. However, the frequency of the said reactions is relatively rare, with a rate in 1 per 10,000 (Cromolyn Sodium Package insert, 2010). Discontinuation or tapering the dose of cromolyn may result in rebound symptoms; therefore, patients should exercise caution. Cromolyn is a pregnancy category B medication, and the manufacturer recommends caution in use in breast-feeding mothers as adequate evidence proving safe use in this population is lacking.

Drug Interactions

No known drug interactions exist.

Conclusion

The intranasal mast cell stabilizer, cromolyn sodium, is administered for prophylaxis of allergic rhinitis and can require up to 2 weeks of use for full clinical effect. This agent is well tolerated with limited side effects and has no known clinically significant drug interactions. The medication is available over the counter without the need of a prescription. Due to potential adherence problems and limited efficacy compared to intranasal corticosteroids, intranasal cromolyn sodium may have a limited role in therapy. Cromolyn may be a considerable option to treat allergic rhinitis in patients who cannot tolerate other intranasal allergy medications or when drug interactions may be of significant concern.

Cross-References

- ▶ Activating and Inhibitory Receptors on Mast Cells
- ▶ Intranasal Anticholinergics
- ▶ Intranasal Antihistamines
- ▶ Intranasal Corticosteroids
- ▶ Intranasal Decongestants
- ▶ Mast Cell Mediators
- ▶ Mast Cells, Growth and Development
- ▶ Morphology and Histologic Identification of Mast Cells
- ▶ Oral Mast Cell Stabilizers

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Intraocular Vasoconstrictors

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Synonyms

Intraocular decongestants; Ocular vasoconstrictors; Sympathomimetic amines

Definition

Allergies affect 15 % of the world population and up to 30 % of the US population, with the majority of these individuals having ocular involvement (Bielory 2000). Seasonal allergic and nonallergic conjunctivitis are the most

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common ocular allergies (Bielory 2000). The direct costs associated with allergic conjunctivitis in the United States have been estimated to be $5.9 billion; with a quarter of these costs attributable to direct medication expense (Bielory 2002a). Allergic conjunctivitis is associated with symptoms of tearing, redness, itching, conjunctival swelling, and eyelid edema (Collum and Kilmartin 2000). The symptoms can range in severity and duration. For some individuals, the symptoms can last less than 24 h (acute), for the duration of a particular pollen season (seasonal), or throughout the year (perennial). Ocular decongestants are often used temporarily to help manage these symptoms and can be used in conjunction with ocular antihistamines and mast cell stabilizers.

The symptoms of allergic conjunctivitis are caused by environmental factors that cause mast cell degranulation in the conjunctiva. This causes the release of vasoactive mediators, such as histamine, prostaglandin D2, and leukotriene C4, which induces vascular permeability and vasodilation (Greiner and Udell 2005) (Mishra et al. 2011). The symptoms that can be bothersome to most individuals are ocular redness and itching (Greiner and Udell 2005).

Mechanism of Action

Ocular decongestants provide temporary symptomatic relief of allergic conjunctivitis but have no effect in decreasing the allergic response (Bielory 2002b). These medications are categorized as sympathomimetic amines because they imitate the effects of norepinephrine and epinephrine and act on α1 and α2 receptors. Tetrahydrozoline, oxymetazoline, and naphazoline are classified as imidazole derivatives and differ from the adrenergic agonist phenylephrine in that it has more affinity to the alpha receptor than beta adrenergic receptors (Adamczyk and Jaanus 2008). Sympathomimetics cause vasoconstriction of the ocular blood vessels, thus leading to decreased capillary leakiness in the eye and, therefore, diminishing or resolving symptoms such as tearing, redness, conjunctival swelling, and eyelid edema.

Drug Information

Please refer to Table 1, Drug information for intraocular vasoconstrictors, for a summary of generic and brand names, dose strengths available, prescription status, and dosing. Table 2, Pharmacokinetics for common intraocular vasoconstrictors, provides a summary of the pharmacokinetic properties of the products.

Clinical Trials

Intraocular vasoconstrictors are typically used to reduce hyperemia associated with eye irritation and/or allergic conjunctivitis. To date, there are limited published reports regarding efficacy in the relief of hyperemia associated with this class of medications. Ocular hyperemia is often short-lived and difficult to reproduce in order to quantify benefit from pharmacologic modification (Abelson and Smith 2012).

A randomized double-masked placebo study by Greiner and colleagues evaluated the relative effectiveness of pheniramine/naphazoline 0.3 %/0.025 % combination plus olopatadine 0.1 % solution versus the individual product plus placebo using the ocular allergy index (Greiner and Udell 2005). Eighty-three subjects were randomly assigned to one of the three treatment groups and given this medication 10 min before the conjunctival allergen challenge. Subjects were evaluated at 7, 12, and 20 min after the allergen challenge to assess the eyelid swelling, itching, and erythema in the ciliary and episcleral vessel bed. Each symptom was scored on a 0–4 point scale (except eyelid swelling which was scored out of 3 points), with 4 being the most severe symptom. The possible ocular allergy symptom score ranged from 0 to 23. Pheniramine/naphazoline plus olopatadine had statistically lower ocular allergy scores than the individual products plus placebo ($P < 0.001$). Additionally, the ocular allergy score with pheniramine/naphazoline was lower than that of olopatadine at 12 and 20 min ($P = 0.005$ and $P = 0.001$, respectively). The authors conclude that the combination of an antihistamine plus an

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Intraocular Vasoconstrictors, Table 1 Drug information for intraocular vasoconstrictors

Active ingredient	Common brand name (company)	Strength	Prescription or OTC	Dosing adults and children >6
Naphazoline	All Clear® (Bausch & Lomb)	0.012 %	OTC	0.01–0.03 % solution: instill topically to the conjunctiva four times daily
	Clear Eyes® (Prestige Brands)			
	Naphcon® (Alcon)	0.03 %	OTC	
	All Clear-AR® (Bausch & Lomb)	0.1 %	Prescription	0.1 % solution: instill 1–2 drops to the conjunctiva every 3–4 h as needed (max 4 doses/day)
	AK-Con® (Akorn)			
	Albalon® (Allergan)			
Oxymetazoline hydrochloride	Visine L.R.® (Pfizer)	0.025 %	OTC	Instill 1–2 drops into affected eye; may repeat every 6 h as needed
Phenylephrine	Ocu-Phrin® (Ocumed)	0.12 %	OTC	0.12 % solution: instill 1–2 drops up to four times daily
	Relief® (Allergan)	2.5 %	Prescription	
	AK-Dilate® (Akon)			
	Mydfrin® (Alcon)			
	Neo-Synephrine® (Sanofi-Aventis)			
	Ocu-Phrin(Ocumed)			
	AK-Dilate®(Akorn)	10 %	Prescription	
	Neo-Synephrine® (Sanofi-Aventis)			
	Ocu-Phrin® (Ocumed)			
Tetrahydrozoline chloride	Collyrium Fresh® (Bausch & Lomb)	0.05 %	OTC	Instill 1–2 drops to the conjunctiva up to four times daily
	Murine Plus® (Prestige Brands Holdings)			
	Visine Moisturizing® (Pfizer)			

OTC over the counter
McEvoy (2006b)

ocular decongestant was more effective than the mast cell stabilizer, olopatadine, in relieving the symptoms of allergic conjunctivitis.

Adverse Effects

The alpha-1 agonist properties of intraocular vasoconstrictors are generally benign due to local ophthalmic administration. This class of medications has a potential for tachyphylaxis, rebound effects, and tolerance. Case reports by Spector et al. have demonstrated that rebound hyperemia may persist despite discontinuation of intraocular vasoconstrictors (Spector and Raizman 1994). Additionally, studies have shown that systemic naphazoline ingestion may lead to hypertension, bradycardia, diaphoresis, and acute pulmonary edema (Fukishama et al. 2008).

Drug Interactions

Phenylephrine (when given in concentrations greater than 2.5 %) and naphazoline can be systemically absorbed, and interaction with monoamine oxidase inhibitors (MAOI) can occur to potentially cause severe hypertension. Careful supervision and dose reduction is required if using phenylephrine within 21 days after the patient has received a MAOI (McEvoy 2006a).

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Intraocular Vasoconstrictors, Table 2 Pharmacokinetics for common intraocular vasoconstrictors

Active Ingredient	Absorption	Distribution	Metabolism	Excretion	Duration of action
Naphazoline	Rapid absorption; onset 10 min	Data not available in humans	Unknown	Data not available in humans	2–6 h
Oxymetazoline hydrochloride	Rapid absorption onset 5–10 min	Data not available in humans; with high doses systemic distribution can occur	Unknown; Evidence of CYP2C19 metabolism in liver if systemically absorbed	Data not available in humans	Vasoconstriction may persist for up to 6 h
Phenylephrine	Rapid absorption; vasoconstriction occurs almost immediately	Data not available in humans; with high doses systemic distribution can occur	Metabolism occurs in liver and intestine by monoamine oxidase	If systemically absorbed 80 % of metabolites are eliminated in the urine	30 min to 4 h
Tetrahydrozoline chloride	Rapid absorption; onset occurs in minutes	Data not available in humans; with high doses systemic distribution can occur	Unknown	Data not available in humans	4–8 h

McEvoy (2006b)

Conclusion

Intraocular vasoconstrictors are temporarily used for the symptomatic relief of allergic conjunctivitis. Most intraocular vasoconstrictors are available as over-the-counter preparations. A major consideration for this drug class is the potential for tachyphylaxis and medicamentosa in the eye. For this reason, the recommended duration of use is limited to 3 days.

Cross-References

► Oral Decongestants

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Laboratory and Assay Evaluation

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Synonyms

Calibration; CLIA; Proficiency testing; Quality assurance

Definition

The clinical laboratory operation and the level of specific assay performance are governed by laws that differ among various countries. Among these regulations are requirements for specific training and education by the director and staff, establishment of a laboratory quality assurance and assay quality control program, and expectations regarding the validation and calibration of assays performed in the laboratory. An American diagnostic allergy laboratory will be used as an illustrative model for this discussion.

Introduction

The operation of clinical laboratories is governed by laws prepared by governments of different countries. In the United States, staff qualifications, the operation of a clinical laboratory, proficiency testing and quality assurance, and the required record keeping are defined in the Federal Register by the Clinical Laboratory Improvement Act (CLIA) of 1967. The act was updated with amendments in 1988 and 1990 in 42 CFR Part 74 (Medicare, Medicaid and CLIA Programs: Revision of Laboratory Regulations; Final Rule with Request for Comments). The laboratory is defined as an entity for the biological, biophysical, immunohematological, microbiological, serological, chemical, hematological, cytological, pathological, or other examination of materials derived from the human body, for the purpose of providing information for the diagnosis, prevention, or treatment of any disease or the assessment of the health of human beings. It provides detailed guidelines on the administration, proficiency testing, quality assurance, inspections, and record keeping.

Laboratory Administration

A clinical laboratory in the USA must be accredited by the Joint Commission on the

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Accreditation of Healthcare Organizations or other recognized entities such as the College of American Pathologists. All personnel, including individuals who collect specimens, must be licensed or meet applicable standards that are required by US State and local laws. Many states in the United States require separate clinical laboratory licenses even when testing is performed on specimens collected in their state but tested in other states. The laboratory must comply with all fire safety and environment and health laws regarding the storage, handling and disposal of chemical, biological, and radioactive waste.

Proficiency Testing

Laboratory proficiency testing involves participation in an independent (non-manufacturer sponsored) program in which challenge specimens (e.g., serum) are sent to participating clinical laboratories to be evaluated in assays that measure a relevant panel of analytes. An illustration of a proficiency testing for diagnostic allergy laboratories in North America is the College of American Pathologists' SE (Diagnostic Allergy) survey in which five or six challenge sera from atopic patients are sent every 17 weeks (three times a year) to over 150 laboratories to be analyzed for total and allergen-specific IgE (Hamilton 2010). The results are returned to the College of American Pathologists which computes the performance of a given laboratory for a particular analyte such as total IgE or allergen-specific IgE in relation to peer laboratory performance. For quantitative assays that involve a calibration curve (see below), mass units per volume are statistically analyzed as the mean, standard deviation, and coefficient of variation. These statistics are provided to the laboratories and accrediting agencies in the form of a participant's summary which provides an ongoing assessment of the laboratory's accuracy and interlaboratory reproducibility in relation to its peer groups that measure the same analyte using either the same and different assay methods.

The laboratory uses internal control material, which is a solution, lyophilized preparation, or pool of collected human specimens, or artificially derived materials that are intended to assess reproducibility of the assay's measurements over time. The control serum is designed to contain a matrix similar in ionic charge, density, pH, and protein content to that of the test specimens (see ▶ Diagnostic Assay Components). It serves as the primary quality control check on the validity of the calibration–reference curve, the assay reagents, and equipment. Moreover, it permits the laboratory staff to evaluate the interassay variation using values obtained from many assay runs. A range of measured analyte values (2 standard deviations (SD) and a 95 % confidence interval) are computed for the control specimen and they are plotted in a Levey–Jennings quality control chart to identify assays that are in or out of control with shifts and trends in the measured values.

Quality Control

In the diagnostic allergy laboratory, a daily intralaboratory quality control program for total serum IgE assays commonly involves the analysis of three control sera for which there are well-documented IgE ranges. Typically, concentrations of the IgE in the control sera cover the low (1–10 kU/L where 1 unit (U) = 2.4 ng of IgE), medium (50–100 kU/L), and high (1,000–2,000 kU/L) regions of a total serum IgE assay's calibration curve. A problem with the assay is identified when one or more internal control specimens produce a result that is out of the expected 2 SD control range as defined by 10–15 previous assays. For some automated assays, singlicate measurements have been shown by the manufacturer and the laboratory to be acceptable because of highly reproducible assay results (Matsson et al. 2008).

For allergen-specific IgE antibody assays, there are two schools of thought on what constitutes a proper internal quality control program. In the first (less used) program, each of the ~200 allergen-containing reagents involving different specificities is viewed as a separate unique test that needs its own specific IgE quality control

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serum which is tested in each assay. This strategy does not appreciate the extensive stability and quality control testing that is performed by the manufacturer on each allergen-containing reagent before it is released for use. Moreover, this strategy is impractical and costly in that it requires each laboratory to maintain a serum bank of IgE-positive sera for every allergen specificity. The more widely used quality control approach considers the IgE antibody assay as a system that employs several hundred allergen-containing reagent "components" of different specificities. Each allergen-containing reagent is thus considered successfully quality controlled by the manufacturer, and the user must simply validate the calibration curve and analytical threshold limit of the qualitative assay. This can be accomplished by the analysis of three sera containing high, medium, and low levels of IgE antibody, in a manner similar to those used in the total serum IgE assay. In addition, laboratories identify a group of 5–15 common allergen specificities (e.g., peanut, common ragweed, oak tree, *Alternaria tenuis*, cat dander, and *Dermatophagoides pteronyssinus*) for which IgE antibody-containing human sera are plentiful. A large serum pool is then prepared that contains IgE antibody to all the specificities, and it is analyzed against each of the allergen-containing reagents spread throughout each assay run (Matsson et al. 2008). This specific IgE antibody-testing program provides confirmation of the calibration portion of the assay, and it validates the other common reagents that may be exclusively used in the allergen-specific IgE portion of the assay.

Assay Validation

In the United States, assays that are used by clinical laboratories to generate results which are used in patient management need to be cleared by the Food and Drug Administration. A "*predicate device*" is identified that is an assay for the in vitro measurement of an allergen-specific IgE antibody that has been previously validated and thus cleared for marketing by the FDA. The performance of a new assay is compared in terms of its analytical sensitivity and analytical specificity in direct comparison with a predicate assay.

One of the assay performance variables that is examined when validating an assay is the issue of *cross-reactivity*. In an immunology test, cross-reactivity involves the reaction of an antibody with an antigen other than that which elicited its formation, as a result of shared, similar, or identical antigenic determinants. Within the context of IgE antibody assays, cross-reactivity generally refers to a human IgE antibody that binds to an allergenic epitope which is structurally similar to, but not identical with, the molecule that elicited its formation. This binding results from the recognition of shared, similar, or identical allergenic determinants by IgE antibodies. In addition, cross-reactivity can refer to the degree to which the antihuman IgE detection reagents bind to other human immunoglobulin isotypes (IgG, IgA, IgM, IgD).

Assay Calibration

In the diagnostic allergy laboratory, early IgE antibody measurements were considered qualitative in that they produced a positive or negative result based on the level of the response signal measured in comparison to a preassigned positive threshold level. Gradually, semiquantitative assays emerged in which both a positive/negative result and the magnitude of the signal measured as an arbitrary class score were reported. The magnitude of the response signal detected in the assay was related in terms of rank order to but not directly proportional to the quantity of IgE antibody present in serum. Today, these reporting schemes are out of date and should not be used. Current IgE antibody assays employ a calibration portion which defines the dose–response relationship of the assay. Thus, response results obtained by testing patients' sera are interpolated in dose units that relate to the relative quantity of IgE antibody in a serum.

Both *homologous and heterologous interpolation* methods have been used in the calibration portion of IgE antibody assays (Butler and Hamilton 1991). *Homologous interpolation* is

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a procedure that maximizes assay parallelism and the assay's working range by using the same solid-phase allergen specificity throughout the assay. The calibration curve is generated with a human IgE antibody-containing serum of the same allergen specificity as is detected in the test sera. Thus, the IgE antibody-containing reference serum pool typically dilutes out in the same manner (in parallel) with the test serum IgE antibody. The primary difficulty with this approach is the need for liter quantities of human serum pools that contain IgE antibody specific for each of the over 200 allergen specificity run in the laboratory. To address the problem of obtaining large calibrator stocks, heterologous interpolation was adopted in which a total IgE calibration curve that is traceable to the WHO 75/502 IgE primary standard is used to interpolate quantitative IgE antibody results involving hundreds of different allergen specificities. The heterologous interpolation system is now the industry standard for commercially available allergen-specific IgE assays. Heterologous interpolation from a total IgE calibration curve has permitted the IgE antibody assays to produce accurate and reproducible estimates of the concentration of IgE antibody.

Occasionally, depletion analysis is performed to estimate the quantity of IgE antibody in the calibration process of a prospective reference serum. Using peanut as an illustrative allergen specificity, a potent IgE anti-peanut containing serum is first optimally pre-absorbed with either peanut-solid phase or a sham-solid phase. Three sera (unabsorbed, sham-absorbed, and peanut-absorbed) are then analyzed in a total serum IgE for their IgE content. Difference in the total IgE levels between the sham- and peanut-absorbed serum is assumed to be the amount of specific IgE that was depleted or removed from the serum by the solid-phase allergen. The sham-adsorbed IgE antibody levels should be equivalent to unabsorbed serum levels. Elution of the peanut-solid phase adsorbed IgE antibody can be added to the procedure to further validate the efficiency of the extraction procedure and provide an additional level of confidence in the specific antibody estimation.

Summary

A clinical laboratory is governed by defined expectations involving their staff, methods, and procedures that are established by governmental regulatory agencies. These regulations define the qualifications of the director and technical staff, the level of external proficiency testing required to verify good performance of their procedures, the internal quality control practices that are expected for each assay, and the level of overall assay validation. The performance of each assay depends on its calibration system that uses either homologous calibrators in the case of total serum IgE assays or heterologous interpolation methods in the case of IgE antibody assays.

Cross-References

- ▶ Analytes and Biomarkers: IgE
- ▶ Cow's Milk Allergy
- ▶ Diagnostic Assay Components
- ▶ Egg Allergy
- ▶ Food Allergies, Diagnostic Testing
- ▶ Food Allergy, Overview
- ▶ IgE Testing
- ▶ Imported Fire Ant Allergy
- ▶ Peanut Allergy

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Leukotriene Modifiers

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Synonyms

Anti-leukotriene; Leukotriene receptor antagonist; Leukotriene receptor blocker; Leukotriene inhibitor; Leukotriene synthesis inhibitor

Definition

Leukotrienes (LTs) are defined as lipid mediators that play an important role in the pathophysiology of inflammatory respiratory disorders. These substances can be divided into two distinct categories consisting of LTB_4 and cysteinyl LTs, LTC_4, LTD_4, and LTE_4. Leukotrienes are potent bronchoconstrictors, promote respiratory permeability, and increase mucus secretion in the airways (Montuschi 2010). Leukotriene modifiers represent a novel therapeutic class approved for reactive airway disorders such as perennial and seasonal allergic rhinitis (AR). They are also used for the treatment of asthma, including exercise or aspirin-induced asthma. The leukotriene modifier (LTM) class consists of three agents available in the United States: montelukast, zafirlukast, and zileuton (Scow 2007). Montelukast is the only leukotriene modifier that has been FDA approved for the relief of symptoms of AR: seasonal allergic rhinitis (SAR) in patients 2 years of age and older, and perennial allergic rhinitis (PAR) in patients 6 months of age and older. Table 1 depicts indications and common dosing for adults and pediatrics for each leukotriene modifier. Due to their mechanism of action, montelukast and zafirlukast are further described as leukotriene receptor antagonists (LTRAs).

Mechanism of Action

Leukotrienes are synthesized from components of the phospholipid cellular membrane. Synthesis is initiated through activation of the phospholipase A_2 enzyme, which cleaves arachidonic acid from the membrane into fatty acid products. 5-Lipoxygenase mediates a crucial step of LT production through the conversion of fatty acids to an intermediate, 5-hydroperoxyeiocosatetraenoic acid, and then to LTs. Leukotriene production is especially prominent in eosinophils and mast cells due to large endogenous arachidonic acid stores. Of the two known types of LTs, the cysteinyl LTs (CystLTs) are implicated in the development of inflammatory airway disorders. The contribution by LTA_4 and LTB_4 to the development of these disease states is unclear. Both forms of LTs are released into the circulation through carrier proteins following production inside the cell (Montuschi and Peters-Golden 2010).

The CystLTs exert their effect through interaction with two known G-protein coupled receptors, $CysLT_1$ and $CysLT_2$. CystLTs' role in reactive airway diseases is predominantly mediated through $CysLT_1$. This receptor can be found throughout the airway smooth muscles, vascular endothelial cells, macrophages, basophils, and eosinophils. $CysLT_2$ may be implicated in cases of acute, severe asthma; however, this receptor's exact role has not been elucidated. Following binding with the $CysLT_1$ receptor, the CystLTs can cause airway inflammation, hyperplasia, mucosal gland hypersecretion, and collagen deposition throughout the respiratory tract (Montuschi and Peters-Golden 2010).

Attenuating the action of leukotrienes can be accomplished by two separate mechanisms: (1) blocking leukotriene production (zileuton) or (2) antagonizing the leukotriene receptors (montelukast and zafirlukast) (Currie et al. 2005). Zileuton inhibits 5-lipoxygenase, which is upstream in the synthesis pathway, and prevents the conversion to CystLTs. This agent exerts its effect through chelation of iron at

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Leukotriene Modifiers, Table 1 Dosing information of available leukotriene receptor antagonists (Capra et al. 2007)

Generic name	Montelukast	Zafirlukast*	Zileuton*
Brand name	Singluair®	Accolate®	Zyflo®
Dose- allergic rhinitis	≥15 years old: 10 mg/day	≥12 years old: 20 mg twice daily	≥12 years old: 600 mg divided 1–4 times/day
	6–14 years old: 5 mg/day	5–11 years old: 10 mg twice daily	<12 years old: Not approved for use
	6 months to 5 years old: 4 mg/day		

* = Not FDA approved for the treatment of allergic rhinitis

5-lipoxygenase's active site. Following chelation, 5-lipoxygenase loses its reduction potential (Dahlen et al. 2006). Conversely, montelukast and zafirlukast affect the CysLTs by selectively blocking the $CysLT_1$ receptors.

Pharmacokinetics

Leukotriene modifiers are only available as capsules or tablets. Inhalation formulations have been investigated, but no clear benefit has been identified with that particular route of administration (Dahlen 2006). This class of medications displays high protein binding (>99 % for montelukast and zafirlukast and 93 % for zileuton) and undergoes hepatic metabolism and biliary excretion. There are limited drug interactions with the leukotriene receptor modifiers mainly attributed to cytochrome P450 (CYP) interactions. Montelukast is metabolized by CYP3A4 and 2C9, zafirlukast is metabolized by CYP2C9 and inhibits CYP3A4 and 2C9, and zileuton is metabolized by CYP1A2, 2C9, and 3A4 and inhibits CYP1A2. Therefore, there are potential drug interactions, especially with CYP inducers or inhibitors (Van Hoecke 2007). Montelukast is administered once daily; however, zafirlukast is dosed twice daily and zileuton is dosed four times daily. Renal dose adjustments are not required for any of the leukotriene modifiers. In patients with hepatic dysfunction, the montelukast dose should be reduced and zafirlukast's or zileuton's use is not recommended (Scow 2007).

Clinical Uses

Leukotrienes play a key role in the inflammatory process involved in the development of AR. Montelukast is the only leukotriene modifier that is approved for use in the treatment of AR. Multiple randomized, double-blind, placebo-controlled trials have demonstrated that montelukast significantly improves day-time nasal symptoms, such as nasal congestion, rhinorrhea, itching, and sneezing, compared to placebo in patients with seasonal AR (VanHoecke et al. 2007). Montelukast has been shown to improve both day-time eye symptoms and night-time symptoms. The rhinoconjunctivitis quality of life score average and global rating of outcomes by both physicians and patients are also significantly improved in patients receiving montelukast compared to placebo (Meltzer 2002; Nayak and Langdon 2007). Similar benefits are documented in patients with perennial AR (VanHoecke et al. 2007). After initiation of montelukast treatment, symptom improvement typically begins within 1–3 days (Nayak and Langdon 2007). AR is characterized by enhanced eosinophil concentrations in the mucosa. Eosinophils are an important marker of inflammation. Montelukast significantly reduces peripheral blood levels of eosinophils, which provides a therapeutic advantage compared to other AR treatment options (Meltzer 2002). Montelukast and oral antihistamines show comparable reductions in eye and nasal symptoms. However, intranasal corticosteroids are superior to montelukast in improving nasal symptoms. Montelukast has been

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shown to reduce asthma symptoms and decrease beta-2 agonist use in patients with concurrent asthma and AR. Clinical studies investigating zafirlukast's and zileuton's efficacy in AR are limited (Van Hoecke et al. 2007); therefore, montelukast is the only leukotriene modifier that has been FDA approved for the relief of symptoms of AR: SAR in patients 2 years of age and older, and PAR in patients 6 months of age and older.

Leukotriene modifiers may have a role in the treatment of other inflammatory disease states such as sinusitis, atopic dermatitis, chronic obstructive pulmonary disease, and allergic conjunctivitis. Further clinical trials are needed before clear recommendations for use can be determined (Riccioni et al. 2004).

Adverse Effects

The leukotriene modifiers demonstrate a favorable safety and tolerability profile. The rate of adverse effects with leukotriene modifiers has not been shown to differ significantly from placebo (Scow et al. 2007). Although adverse effects are uncommon, dry mouth, fatigue, abdominal pain, rash, headache, angioedema, eosinophilia, pruritus, and arthralgia have been documented (Nayak and Langdon 2007).

A potential association exists between leukotriene modifiers and Churg-Strauss Syndrome (CSS), a rare condition of necrotizing vasculitis that typically presents itself following reduction in steroid doses. Most of the reported cases are attributed to successful leukotriene modifier therapy, which leads to decrease in steroid doses. Therefore, the relationship between leukotriene modifier use and CSS is due to the tapering of anti-inflammatory therapy, not to independent use of leukotriene modifiers. However, there have been cases of CSS development during leukotriene modifier therapy without concurrent change in steroid dose (Currie et al. 2005; Nayak and Langdon 2007). Montelukast has been linked to suicidal ideation; however, the rate of suicide-related adverse effects in patients taking montelukast compared to those receiving placebo have been shown to be similar. There is insufficient evidence to prove causation of suicidality with montelukast therapy (Philip et al. 2009).

Phase III trials and post-marketing surveillance revealed that approximately 5 % of patients receiving zileuton display increases in liver enzymes. Upon discontinuation of the medication, the enzymes return to pretreatment levels. To prevent long-term liver toxicity, the manufacturer recommends monitoring liver function tests at baseline, monthly for 3 months, and every 2–3 months thereafter while on zileuton therapy (Scow et al. 2007; Watkins et al. 2007). Reversible increases in liver enzymes and rare reports of liver failure have been documented with the use of zafirlukast, and liver function tests should be monitored every 2–3 months with this medication (Scow et al. 2007).

Summary

LTs play a significant role in the inflammatory process associated with AR. Inhibiting the actions of LTs can be a beneficial strategy in improving control and reducing symptoms. In AR, these agents are comparable to antihistamines in providing symptom improvement. However, leukotriene modifiers are less efficacious than intranasal corticosteroids. The limited adverse effects of these medications make them a well-tolerated therapeutic option in both children and adults for the treatment of AR. Montelukast is the only leukotriene modifier that has been FDA approved for the relief of symptoms of SAR in patients 2 years of age and older, and PAR in patients 6 months of age and older.

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M

mAbs (Omalizumab)

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Synonyms

Anti-IgE; Monoclonal antibody

Definition

Omalizumab is a recombinant humanized monoclonal antibody. It selectively binds to human immunoglobulin E (IgE). Omalizumab inhibits the binding of IgE to the high-affinity IgE receptor (FcεRI) on the surface of mast cells and basophils. As a result the release of mediators and production of cytokines are inhibited. Free serum concentrations of IgE rapidly decline after initiating therapy with omalizumab and are maintained for at least 4 months (Vichyanond 2011). Omalizumab has also demonstrated downregulation of the FcεRI on mast cells, basophils, and dendritic cells (Vichyanond 2011).

Omalizumab and Current Food and Drug Administration (FDA) Approvals

Omalizumab (Xolair®) is currently approved by the US FDA for the treatment of moderate to severe persistent asthma in adults and adolescents (12 years of age and above). Potential patients must have a positive skin test or in vitro reactivity to a perennial aeroallergen and have symptoms which are not adequately controlled with an inhaled corticosteroid (Xolair prescribing information 2010). In other countries omalizumab has an indication for patients 6 years of age and older (Kopp 2011).

While omalizumab does not currently have an indication for the treatment of other allergic conditions, based on its mechanism of action, it may have a role in the treatment of a variety of IgE-mediated diseases. Omalizumab has been reported to have been used in patients with allergic rhinitis, atopic dermatitis, chronic urticaria, and food allergy (Kopp 2011; Vichyanond 2011). Omalizumab has also been reported to have been used in treating patients who have cystic fibrosis in conjunction with allergic bronchopulmonary aspergillosis (Wong et al. 2013).

Omalizumab Dosing

For the treatment of allergic asthma, omalizumab, 150–375 mg, is given subcutaneously every 2 or 4 weeks. The dose is based on the patient's serum total IgE level (IU/mL) and body weight in kilograms. The total IgE level is measured prior to starting therapy with omalizumab. In a dosing nomogram, pretreatment serum IgE levels should be between 30 and 700 IU/mL with body weight between 30 and 150 kg (Xolair prescribing information 2010).

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Omalizumab and Allergic Asthma

A systematic review of placebo-controlled studies was completed to establish the safety and efficacy of omalizumab as add-on therapy to corticosteroids in children and adults with asthma (Rodrigo et al. 2011). The review evaluated 8 trials with 3, 429 total participants. The primary outcomes evaluated included reduction of steroid use from baseline and asthma exacerbations. Asthma exacerbations were defined as hospital admissions, emergency department visits, increased rescue medication, or the use of corticosteroids. The results of this analysis showed that patients treated with omalizumab, when compared with placebo, were more likely able to completely stop their corticosteroid or reduce their total steroid dose by more than 50 %. The analysis also revealed that patients treated with omalizumab had significantly fewer exacerbations per patient compared with patients receiving placebo. With regard to the safety data, there was no difference in the number of withdrawals due to adverse events between the treatment groups. The authors did report more frequent injection site reactions in patients receiving omalizumab. The authors concluded that the efficacy of add-on omalizumab has an acceptable safety profile. They also note that clinical trials of longer duration will be necessary to further evaluate the long-term safety and efficacy of this treatment.

Omalizumab and Allergic Rhinitis

Clinical Trials

In a double-blind, placebo-controlled, randomized, parallel-group study design, the efficacy, safety, and tolerability of omalizumab were investigated in patients who had perennial allergic rhinitis (Chervinsky et al. 2003). The study participants were 12–75 years of age. Following a 2-week run-in period, subjects were randomized to omalizumab or placebo. The dosing strategy for omalizumab was similar to that used for allergic asthma. The primary endpoint was a mean daily nasal severity score which combined sneezing, itchy, runny, and stuffy nose scores. Each symptom was rated by the study participant on a 0–3 point scale with zero being no symptoms and three being severe symptoms. Secondary endpoints included the rhinoconjunctivitis-specific quality of life questionnaire and the use of rescue antihistamines. Two hundred and eighty-nine subjects received at least one dose of omalizumab with 268 subjects completing the trial. Throughout the 16-week treatment period, participants receiving omalizumab had significantly lower nasal severity scores when compared to patients receiving placebo. Additionally, subjects receiving omalizumab had improved scores on the rhinoconjunctivitis-specific quality of life questionnaire and used less rescue antihistamine compared to the placebo group. Overall the study drug was well tolerated with the most frequently reported adverse events being upper respiratory tract infections, headache, and nasopharyngitis. The authors concluded that omalizumab provided effective treatment and was safe and well tolerated in patients with perennial allergic rhinitis.

A second study investigated the safety and efficacy of omalizumab used prophylactically for symptoms of seasonal allergic rhinitis (Casale et al. 2001). In this double-blind, dose-ranging, placebo-controlled trial, participants aged 12–75 years were randomized to receive 50 mg, 150 mg, or 300 mg of omalizumab or placebo subcutaneously every 3–4 weeks for 3–4 treatments. The primary endpoint was the average daily nasal symptom severity score. Study participants recorded symptoms on a daily basis. The symptom scoring scale ranged from 0 (no symptoms) to 3 for severe symptoms. Five hundred and thirty-six participants were randomized. Participants randomized to the 300 mg dose of omalizumab had significantly lower nasal symptom severity scores compared to those participants receiving placebo. The most frequently reported adverse effects associated with omalizumab include headache, upper respiratory infections, and viral infections. There was no difference in the frequency of adverse effects between the omalizumab and

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placebo groups. The authors concluded that omalizumab provided clinical benefits in patients with seasonal allergic rhinitis.

Omalizumab and Other Disease States

At this time the majority of literature evaluating the use of omalizumab in other disease states consists of primarily case reports and uncontrolled studies, which should be interpreted with care (Sanchez et al. 2012). Controlled trials indicate that omalizumab may be a potential therapeutic option for some IgE-mediated disease states particularly urticaria (Maurer et al. 2013a, b).

In a phase 3 trial, the efficacy and safety of omalizumab in participants with chronic idiopathic urticaria who remained symptomatic despite antihistamine therapy were studied (Maurer et al. 2013a). Participants received approved doses of antihistamines. In this international, multicenter, randomized, double-blind, placebo-controlled trial, participants (aged 12–75 years) received three injections of omalizumab or placebo. Participants were randomized to receive a dose of 75 mg, 150 mg, or 300 mg of omalizumab, and the doses were received at 4-week intervals. The participants were followed for an additional 16 weeks. The primary endpoint was the change from baseline in a weekly itch-severity score at week 12. Participants rated their itch-severity score twice daily on a 0–3 scale. Zero indicated no itch while three indicated severe itch. A total of 323 participants were randomized to the trial. The primary endpoint improved in a dose-dependent fashion with participants receiving 300 mg benefitting the most. The 150 mg and 300 mg doses of omalizumab both significantly improved the weekly itch-severity score when compared with placebo. There was no difference in the frequency of adverse events for all groups. However, participants receiving 300 mg did have a higher rate of serious adverse events compared with the other groups (these included melanoma in situ, nephrolithiasis, idiopathic urticaria, and tonsillectomy). The authors concluded that while omalizumab improved the symptoms and signs of chronic idiopathic urticaria, additional work is needed to determine omalizumab's exact role in the treatment of this disease.

A second phase 3 trial evaluated the safety and efficacy of omalizumab in participants with chronic idiopathic/spontaneous urticaria who were currently being treated with antihistamines and/or leukotriene receptor antagonists (Maurer et al. 2013b). Participants were receiving up to four times the approved dose of antihistamine. This was a global, randomized, double-blind, placebo-controlled trial with participants aged 12–75 years. Participants were randomized to receive 300 mg of subcutaneous omalizumab or placebo every 4 weeks for 24 weeks. This was followed by a 16-week observation period. The efficacy endpoints included the change from baseline in mean weekly itch-severity score and number of hives score at week 12. Three hundred and thirty-five participants were randomized. Significant improvements were seen in the efficacy endpoints. Adverse events were similar in both groups. The authors concluded that omalizumab improved symptoms in patients with chronic idiopathic/spontaneous urticaria who were receiving other treatments and was well tolerated.

Omalizumab and Adverse Events

Injection site reactions occur at a rate of 45 % in patients who have received omalizumab. These reactions include bruising, redness, itching, induration, mass, and inflammation. Other adverse reactions reported with omalizumab include arthralgia, pain, fatigue, and dizziness. Additional warnings and precautions included in the prescribing information include malignancy, eosinophilic conditions, and helminth infection (Xolair prescribing information 2010).

Omalizumab does have a boxed warning for anaphylaxis. The frequency of anaphylaxis has been estimated to be approximately 0.09 % (Cox et al. 2007). Anaphylaxis has occurred after the first dose and after a year of receiving

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treatment. The majority of the reactions occur within the first 2 h after the injection; however, some reactions have occurred more than 12 h after receiving the dose of medication. Recommendations to improve patient safety regarding anaphylaxis include counseling the patient on adverse effects of the medication along with signs and symptoms of anaphylaxis, obtaining written consent, reviewing medications to ensure that patients are not taking medications that may interfere with epinephrine, observing patients following an injection for an appropriate period of time, and ensuring patients receive an epinephrine auto-injector with instructions on use (Kim et al. 2010).

Omalizumab and Cost

As with most biological therapies, the cost of omalizumab is considerably higher compared to more conventional pharmacotherapy. While the results of different economical analysis are variable, a review looking at the cost-effectiveness of omalizumab in the treatment of allergic asthma indicates that omalizumab compared well with other biological treatments used for chronic diseases (Sullivan and Turk 2008).

Conclusions

Omalizumab is currently approved in the United States for the treatment of adults and adolescents ($\geq$12 years of age) with moderate to severe persistent allergic asthma. It has an indication in children 6 years of age and older in other countries. It is currently being investigated for the treatment of a variety of IgE-mediated diseases, which at this time do not have approved indications.

Cross-References

- Asthma Variants: Allergic Asthma
- Food Allergy and its Future Treatment
- Role of IgE in Disease
- Urticaria

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Management of Anaphylaxis

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Synonyms

Anaphylactic reaction; Anaphylactic shock; Anaphylactoid reaction; Life-threatening allergy

Definition

It is important to consider both the acute (emergency) and longer-term management of patients; the former aims to reduce the severity of reaction and save life, whereas the latter aims to reduce the risk of further reactions and improve outcomes in the case of further reactions (Walker and Sheikh 2003).

Emergency Management

In fatal episodes, death may occur within minutes, this underscoring the importance of effective, emergency management. The prompt administration of epinephrine (adrenaline) is particularly important, but although potentially lifesaving, evidence indicates that this is underutilized both by patients/carers and professionals, with antihistamines and glucocorticosteroids often preferentially being used (Noimark et al. 2012). In an attempt to support more appropriate emergency management, the forthcoming EAACI Guideline on Anaphylaxis will propose dividing interventions into first-, second-, and third-line management approaches (EAACI Guidelines 2014). Cardiopulmonary resuscitation should be commenced, as necessary, at any time during management.

First-Line Interventions

Adrenaline (epinephrine) is potentially lifesaving and must therefore be administered to all patients experiencing anaphylaxis or who have clinical features indicative of the development of anaphylaxis. It should be given by intramuscular injection into the mid-outer thigh (Resuscitation Council 2008; Sheikh et al. 2012; Simons et al. 2013; EAACI Guidelines 2014). Doses may be repeated at 5-min intervals, as needed. Intravenous administration of epinephrine carries the risk of inducing cardiac arrhythmias and should therefore only be used in by those trained in its use with appropriate facilities for cardiac and hemodynamic monitoring (Rutkowski et al. 2012).

Second-Line Interventions

These include the removal of the trigger and call for help. Patients experiencing anaphylaxis should be put into the recumbent position with their legs elevated or into a comfortable position depending on their presenting features. Sudden changes in posture should be avoided as this may trigger empty ventricle syndrome. Oxygen, fluid support, and short-acting beta-2 agonists given via a nebulizer and a spacer with inhaler may be used to relieve symptoms of bronchoconstriction, particularly in those with food-triggered reactions (Pumphrey 2000).

Third-Line Interventions

H1- and H2-antihistamines may be used as third-line treatment in patients experiencing anaphylaxis to relieve cutaneous symptoms (Lin et al. 2000). There may also be a role for glucocorticosteroids in reducing the risk of delayed, biphasic, or protracted reactions. Biphasic anaphylaxis has been reported to occur in up to 20 % adults, with symptoms recurring within 1–72 h (usually 8–10 h) after the initial reaction has resolved, despite no further exposure to the trigger.

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Discharge Considerations

Patients who present with respiratory compromise should be closely monitored for at least 6–8 h and patients who presented with hypotension require close monitoring for at least 12–24 h before discharge. An experienced physician should be involved in the decision to discharge the patient as there are no definite predictors of biphasic anaphylaxis. Before discharge, the risk of future reactions should be assessed and an epinephrine auto-injector prescribed to those at risk of recurrence. Clear instructions to return to hospital if symptoms recur should be provided; a 1–3-day course of oral glucocorticosteroids may prevent the delayed recurrence of symptoms (Arnold and Williams 2011). Patients should be provided with a discharge advice sheet, including allergen avoidance measures (where possible), and instructions on when and how to use the epinephrine auto-injector; referral should be made to an allergy specialist to investigate possible triggers, assess and, where possible, intervene to minimize the risk of further reactions, and ensure that patients and caregivers are optimally equipped and trained to manage any further reactions. Contact information for patient support groups should ideally be provided to signpost sources of further practically useful information and support (EAACI Guidelines 2014).

Long-Term Management

The long-term management of patients who have experienced anaphylaxis should involve investigations to identify trigger(s), cofactor(s), and treatment(s) that may need to be changed to reduce risk. A risk assessment should be carried out and an epinephrine auto-injector of adequate dose provided, coupled with training in when and how to use this. It is essential to provide an individualized management plan written clearly in simple, nonmedical language which should include a personal identification data; a clear identification of the allergens to be avoided, with allergen avoidance advice; and an anaphylaxis emergency action plan (Nurmatov et al. 2008; Worth et al. 2010). A copy of the plan should be kept by the patient, any caregivers, school staff, and family doctor. A supply of fast-acting, nonsedating, H1-antihistamines can also be useful for treating cutaneous allergic reactions. Consideration should also be given to immunomodulatory treatments in the context of venom- and drug-induced reactions. Psychological support should also be provided as required (EAACI Guidelines 2014; Sheikh and Walker 2005). Regular review and training are important to assess new risks and refresh key messages.

Cross-References

- ▶ Anaphylaxis, Background
- ▶ Anaphylaxis, Clinical Manifestations and Diagnosis
- ▶ Biphasic, Protracted, and Late-Phase Reactions in Anaphylaxis
- ▶ Etiology of Anaphylaxis
- ▶ Mast Cell Mediators Associated with Anaphylaxis
- ▶ Pathophysiology of Anaphylaxis

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Mannitol Challenge

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Definition

Mannitol challenge is a form of indirect bronchial challenge sometimes used in the diagnosis of asthma.

Essay

In 2010, the United States Food and Drug Administration approved mannitol in dry powder form to assess for bronchial hyperresponsiveness in patients 6 years and older. In a mannitol challenge, progressive doses of mannitol are administered as follows: 0, 5, 10, 20, 40, 80, 160, 160, 160 mg. Approximately 1 min after each dose, an FEV1 is obtained. A mannitol challenge is considered positive if the FEV1 decreases by 10 % between two consecutive doses or if it decreases by 15 % or more after a cumulative dose of 635 mg of mannitol (Katial and Covar 2012).

There are two types of challenges, direct and indirect, which are discussed in further detail in the separate entry entitled: *Bronchial Challenges*. The mannitol challenge is an indirect challenge, which means that mannitol acts via inflammatory cells of the airway to indirectly cause bronchoconstriction in a susceptible subject. Because the mannitol challenge is an indirect challenge, it is thought to correlate more closely with airway inflammation than the methacholine challenge. While the methacholine challenge assesses only bronchial hyperresponsiveness, a positive mannitol challenge requires both bronchial hyperresponsiveness and airway inflammation (Katial and Covar 2012). As such, a mannitol challenge would be more likely to be negative in an asthmatic patient whose inflammation is adequately treated with an inhaled corticosteroid or leukotriene-modifying agent, or in a patient with positive methacholine challenge due to airway injury without associated inflammation, as is seen with elite athletes (Koskela et al. 2003; Leuppi et al. 2001; Porsbjerg et al. 2007; Sue-Chu et al. 2010; Liem et al. 2008; Katial and Covar 2012).

A 2010 study comparing these two types of challenges suggests that mannitol challenge has a higher specificity but a lower sensitivity than does methacholine challenge testing. As a result, methacholine challenge might be more appropriate when trying to rule out a diagnosis of asthma, whereas mannitol challenge might be a better test to rule in a diagnosis of asthma. (Sverrild et al. 2010)

For a discussion of contraindications to bronchial challenges, which have been specifically defined for methacholine challenge, please see the separate entry entitled: *Bronchial Challenges*. Medications that might interfere with test results and how long these medications should be held prior to testing are topics discussed in the entry entitled: *Methacholine Challenge*.

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Cross-References

- ▶ Bronchial Challenges
- ▶ Exercise Challenge
- ▶ Methacholine Challenge

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Mast Cell Mediators

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Synonyms

DC; Dendritic cell; FcεRI; High affinity IgE receptor; Leukotriene; LT; Matrix metalloproteases; MMP; Nerve growth factor; NGF; PAF; PG; Platelet-activating factor; PMN; Polymorphonuclear leukocytes; Prostaglandin; TNF; Tumor necrosis factor; Vascular endothelial growth factor; VEGF

Definition

Mast cells are a major source of proinflammatory and immunoregulatory mediators. These molecules include histamine, neutral proteases, lipid mediators and several cytokines and chemokines. Mediators secreted by mast cells play a major role in innate immunity and defense against infection as well as in inflammatory and allergic diseases.

Historical Background

Mast cells exert their effects locally and systemically by releasing a variety of biologically potent mediators, many of which mediate proinflammatory, anti-inflammatory, and/or immunosuppressive functions (Abraham and St John 2010) (Fig. 1). Mast cell activation is induced by a variety of mechanisms, among which the best characterized is binding of multivalent antigen to IgE molecules bound to high affinity IgE receptors (FcεRI) (Rivera et al. 2008). Moreover, mast cell activation con be triggered by other mechanisms, including exposure to anaphylatoxins, stem cell factor, endothelin-1, and various neuropeptides (Galli et al. 2005). Mast cell activation processes, depending on the type and strength of the stimuli (Galli et al. 2005) (Table 1), result in downstream events that lead to the secretion of three classes of mediators: (a) preformed mediators stored in the cells' cytoplasmic granules (degranulation) which involves the fusion of the granules with the plasma membrane; (b) the de novo synthesis of proinflammatory lipid mediators; and (c) the synthesis and secretion of several growth factors, cytokines, and chemokines (Galli et al. 2005; Siraganian 2003).

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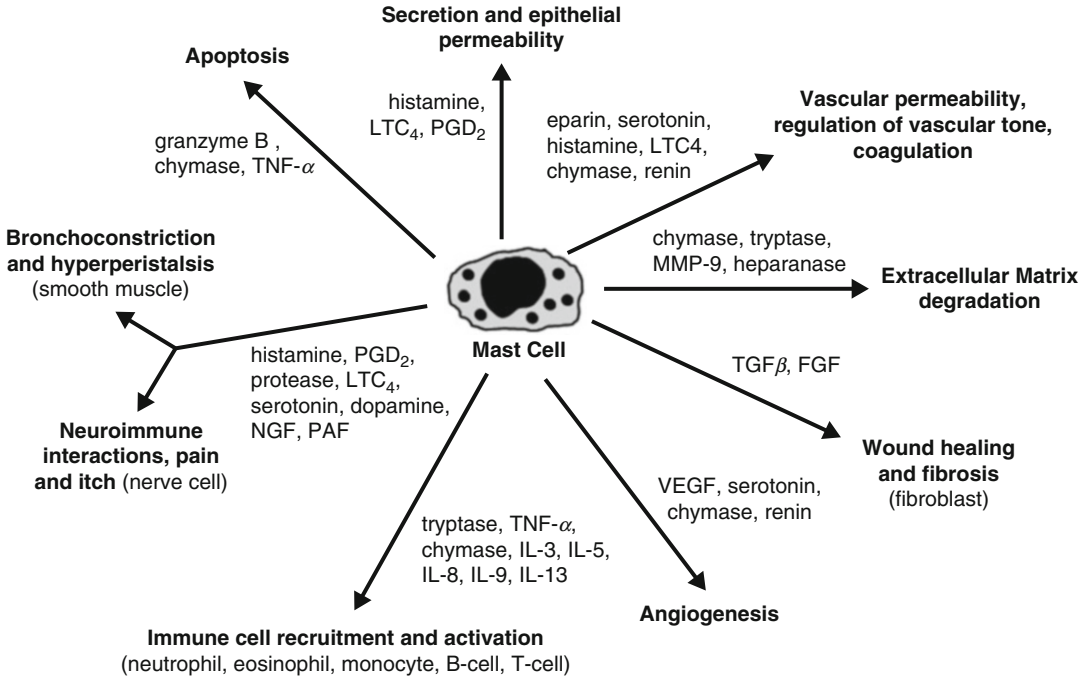
Secretion and epithelial permeability
Apoptosis
histamine, LTC4, PGD2
eparin, serotonin, histamine, LTC4, chymase, renin
Vascular permeability, regulation of vascular tone, coagulation
granzyme B , chymase, TNF-α
Bronchoconstriction and hyperperistalsis (smooth muscle)
chymase, tryptase, MMP-9, heparanase
Extracellular Matrix degradation
Mast Cell
histamine, PGD2, protease, LTC4, serotonin, dopamine, NGF, PAF
TGFβ, FGF
Neuroimmune interactions, pain and itch (nerve cell)
Wound healing and fibrosis (fibroblast)
VEGF, serotonin, chymase, renin
tryptase, TNF-α, chymase, IL-3, IL-5, IL-8, IL-9, IL-13
Angiogenesis
Immune cell recruitment and activation (neutrophil, eosinophil, monocyte, B-cell, T-cell)

Mast Cell Mediators, Fig. 1 Mast cells release either preformed and de novo synthesized mediators, which exert a wide spectrum of effects on several cells and tissues

Mast Cell Mediators, Table 1 Mast cell activation

Major stimuli of mast cell	*Mast cell response*
Cross-linking of IgE	Release of stored mediators, cytokines, chemokines, and lipid mediators
Toll-like receptor ligands	Secretion of cytokines, chemokines, and lipid mediators
Neuropeptides, venom components, and products of complement activation	Degranulation with rapid release of stored mediators, but for some agonists, lower secretion of lipid mediators and cytokines
Bacterial and viral products	Secretion of cytokines and chemokines, but for some pathogens, little or no degranulation

Mast Cell Mediators, Table 2 Major preformed mediators stored in mast cell granules

Biogenic amines	Histamine, Serotonin, Dopamine
Lysosomal enzymes	β-hexosaminidase, β-glucuronidase, β-D-galactosidase, arylsulfatase A, cathepsin C, cathepsin B, cathepsin L, cathepsin D, and cathepsin E
Glycosaminoglycans	Heparin
Proteases	Chymase, tryptase, cathepsin G, granzyme B, MMP-9, renin
Cytokines	TNF-α IL-4, TGF-β bFGF-2, IL-15, NGF, VEGF, stem cell factor
Others	heparanase, peroxidase, LL-37/cathelicidin

Preformed Mediators

Secretory granules of mast cells contain preformed mediators that are rapidly (within seconds to minutes) released into the extracellular environment upon cell stimulation. These mediators include biogenic amines, lysosomal enzymes, proteases, proteoglycans, and cytokines (Table 2). They are responsible for many of

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Mast Cell Mediators, Table 3 Effects of histamine on the cells

Effects	*Involved receptors*
Increase in vascular permeability	H1 and H2
Contraction of smooth muscle	H1
Promotes prostaglandin production	H1
Increases PMN* chemokinesis	H1 and H4
Increases eosinophil C3b receptor expression	H1
Increases fibroblast and endothelial cell growth	H1
Stimulates suppressor T lymphocytes	H2
Decreases basophil histamine release	H2
Decreases lymphokine release	H2
Decreases PMN migration	H2
Increases gastric acid production	H2
Increase mast cell chemotaxis	H2 and H4
Enhance mucus production	H1 and H2
Stimulate neurons	H1 and H3
Modulation of immune responses	H4

the acute signs and symptoms of mast cell-mediated allergic reactions, including edema, bronchoconstriction, increased vascular permeability, angiogenesis, inflammatory cell recruitment, etc.

Histamine is the best known mast cell–derived mediator. Histamine release is a hallmark of mast cell degranulation (Riley 1953) occurring upon immunologic and nonimmunologic activation (Lowman et al. 1988). Histamine is synthesized by decarboxylation of histidine, in a reaction catalyzed by histidine decarboxylase. The main effects of histamine are mediated through four distinct receptors located on target cells and are schematically reported in Table 3.

Heparin is another preformed mediator synthesized and stored in the granules of mast cells (Lundequist and Pejler 2011). Heparin released into the tissues by activated mast cells exerts several functions. Heparin binds to antithrombin III and platelet factor IV, decreases complement activation, increases endothelial cell migration, binds fibroblast growth factors, increases release of plasminogen activator, phospholipase A_2, and triglycerides, promotes fibronectin binding to collagen and regulates tryptase, chymase, and neutrophil elastase activity.

Mast cells granules are a major storage site for proteases which constitute more than 30 % of the total mast cell protein (Hart 2001). Mast cell proteases are stored as active enzymes and their expression differs among mast cell in different tissue and species (Lundequist and Pejler 2011). The two main proteases, tryptase and chymase, are biomarkers of local and systemic mast cell degranulation and anaphylaxis. Chymase is expressed only in a subset of mast cells in the lung and gut. Although some proteases indeed augment allergic inflammation (Waern et al. 2009) and their inhibition is a potential pharmacological target in asthma and related allergic disorders, they are protective and even anti-inflammatory in some settings. For example, mast cell tryptases may protect from serious bacterial infections (Thakurdas et al. 2007). Chymases help to maintain intestinal barrier function and to eliminate parasitic worms and may support blood pressure during anaphylaxis by generating angiotensin II. Furthermore, chymase cleaves epidermis from dermis, degrades substance P and bradykinin, induces tumor cell cytotoxicity, decreases keratinocyte and fibroblast growth. Tryptase degrades fibrinogen, Hageman's factor, calcitonin gene–related peptide and vasoactive intestinal polypeptide, increases fibroblast proliferation, and activates pro-stromelysin 3.

Mast Cell Lipid Mediators

Arachidonic acid mobilized by cytosolic phospholipase A_2 in activated mast cells is rapidly converted to eicosanoids (Boyce 2007), such as prostaglandins (PGs) and leukotrienes (LTs). Mast cells are a major source of platelet-activating factor (PAF), a biologically active phospholipid involved in anaphylaxis (Vadas et al. 2008). PGD_2 and LTC_4 are both potent bronchoconstrictor and vasodilatatory molecules with a resultant increase in vascular

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permeability. They also have significant effects on antigen presentation, matrix deposition, fibrosis, and activation of eosinophils (PGD_2, LTB_4, PAF) and neutrophils (PGD_2, PAF, and LTB_4) (Henderson et al. 1996; Kabashima et al. 2003).

Mast Cell Cytokines, Chemokines, and Growth Factors

It is clearly established that human mast cells can produce a wide spectrum of multifunctional cytokines, chemokines, and growth factors, many of which can participate in the transition from innate immunity to adaptive immunity (Galli et al. 2005). Moreover, it was demonstrated that certain cytokines and growth factors can be released from both preformed (Table 2) and newly synthesized pools. Cytokine and chemokine production by mast cells is closely regulated and may occur independently of classical mast cell degranulation. Depending on the nature of the stimulus or type of infection, a unique profile of cytokines is generated. Several studies have shown that mast cell cytokines and chemokines regulate dendritic cell (DC) migration, maturation, and function. TNF-α and IL-1 facilitate the migration and functional maturation of DCs (Steinman and Inaba 1999), and other potential products of mast cells, including IL-16, IL-18 (Cumberbatch et al. 2001), CCL5 and prostaglandin E2 can also promote DC migration. Mast cell–derived TNF-α and exosomes can upregulate expression of integrins, MHC class II, CD80, CD86, and CD40, thereby promoting functional maturation of DCs (Skokos et al. 2003). Mast cell–derived thymic stromal lymphopoietin (TSLP) and IL-17E may also contribute to the modulation of DC function in the setting of TH2-associated immune responses.

Many molecules, including adhesion molecules and chemokines, can critically influence T cell recruitment to sites of inflammation. Mast cells are often located in close proximity to T cells at sites of allergic reactions and in other immunological responses (Mekori 2004), where they can promote T cell migration either directly, by producing chemotactic factors such as IL-16, CXCL1, CCL2, CCL3, CCL4, CCL5, CCL20, CXCL10, or LTB4, or indirectly, by upregulation of expression of cell surface adhesion molecules, such as E-selectin, intercellular adhesion molecule 1, and vascular cell adhesion molecule 1, on endothelial cells.

Moreover, mast cells also express cytokines that influence B cell development and switch to IgE production, such as IL-4, IL-6, and IL-13, and promote eosinophil maturation, like IL-5, and eosinophil and neutrophil chemotaxis, like eotaxin (CCL11) and IL-8.

Mast cell play a pivotal role in the angiogenesis and lymphangiogenesis processes through the release of angiogenic factors (Detoraki et al. 2009). Angiogenesis is an important feature of chronic inflammation and cancer development. Levels of angiogenic factors, including VEGF-A, are increased in the airways of asthmatic subjects and their expression and the extent of neovascularization significantly correlate with asthma severity (Chetta et al. 2005).

Cross-References

- IgE Receptor
- Mast Cells

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Mast Cell Mediators Associated with Anaphylaxis

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Synonyms

Anaphylactic reaction; Anaphylactic shock; Anaphylactoid reaction; Life-threatening allergy

Definition

Serial measurements of serum mast cell tryptase (MCT) in venom- and drug-induced reactions can be helpful, but these are less useful if reactions are triggered by foods as shock is less common. As tryptase has a short elimination half-life, serial measurements taken 15–180 min after the acute episode have been shown to improve test specificity when compared to individual measurements (Fig. 1 below). A raised baseline value suggests mastocytosis (Simons and Sheikh 2013). Other laboratory tests of interest include plasma histamine or urinary histamine metabolites; the latter is not reliable as its levels are affected by diet and

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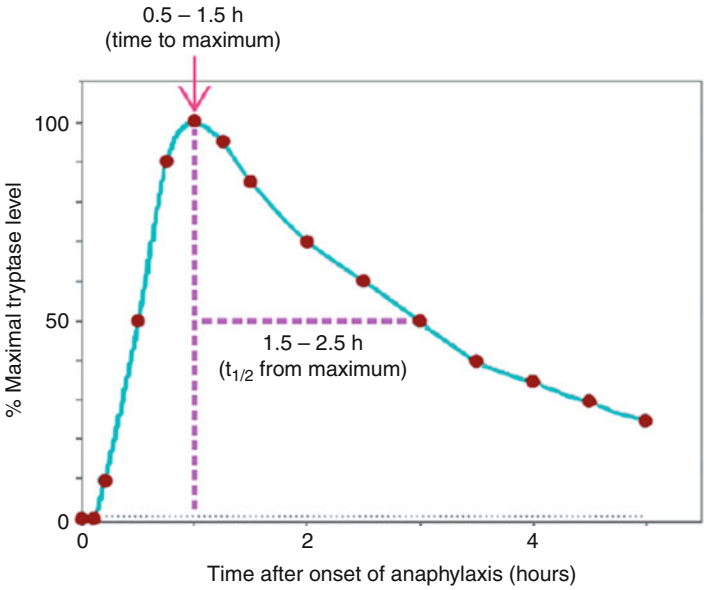

Mast Cell Mediators Associated with Anaphylaxis, Fig. 1 Suggested time course for the appearance of tryptase in serum or plasma during systemic anaphylaxis (Source: Reprinted with permission from Elsevier)

bacteria in the urine (Simons 2008). Low levels of the PAF acetylhydrolase have been reported in fatal anaphylaxis, and failure of this enzyme to inactivate PAF may help identify individuals at risk of very severe or even fatal anaphylaxis (Vadas et al. 2008).

Cross-References

- ▶ Anaphylaxis, Background
- ▶ Anaphylaxis, Clinical Manifestations and Diagnosis
- ▶ Biphasic, Protracted, and Late-Phase Reactions in Anaphylaxis
- ▶ Etiology of Anaphylaxis
- ▶ Management of Anaphylaxis
- ▶ Pathophysiology of Anaphylaxis

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Mast Cells

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Synonyms/Mast Cell Subtypes

Tryptase-/chymase-positive (MC_{TC}); Tryptase-positive (MC_T)

Definition

Mast cells (MC) are immune cells sparsely distributed in the connective tissues and organs (e.g., skin, lung, gut, and heart) and are seemingly strategically placed around blood vessels and nerves. Mast cells are of bone marrow origin and have been shown to respond to danger signals of innate and acquired immunity with immediate and delayed release of inflammatory mediators.

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Historical Background

In 1878, Paul Ehrlich was the first to describe mast cells as a result of their numerous and prominently stained cytoplasmic granules that appeared when stained with basic stains (e.g., Alcian blue, toluidine blue). Hence, their name is derived from the German word "mastzellen" because they looked to be well fed or "fattened" cells (Ehrlich 1877). Their appearance resembles that of blood basophils, but they differ with regard to two noticeable morphologic features: (1) they contain many more cytoplasmic granules of uniform size, and (2) the nucleus seen in mast cells is typically oval in shape and not segmented like that seen in basophils. In addition, the staining properties attributed to mast cells result from the heparin sulfate-rich glycosaminoglycan content of their granules, rather than the chondroitin sulfate-rich content in the granules of basophils. Mast cells are of bone marrow origin but are released into circulation as stem cell factor (SCF)-dependent pro-mastocyte intermediates. Final maturation into mast cells occurs at the organ site where they then take up residence. Their half-life in tissue is estimated to be on the order of months. The inflammatory mediators within their granules are indicative of a role in allergic disease and anaphylaxis, but numerous other biological roles have been indicated, including cancer (mastocytosis), autoimmunity, reproductive disorders, tissue remodeling during chronic inflammation, and even the potential to downregulate inflammation (Hsu and Boyce 2009).

At least two subtypes of mast cells have been defined in humans based on their anatomical location and expression pattern of specific granule-associated proteases (Irani et al. 1989). Those designated as tryptase-positive mast cells (MC_T) are typically found in mucosal tissues such as the lung alveoli and intestine. Those mast cells additionally expressing chymase, carboxypeptidase A, and cathepsin G (MC_{TC}) are generally found in the skin, blood vessels, submucosa, and synovium. Mouse models have indicated that the development of the MC_T subset is T cell dependent, possibly requiring specific cytokines in order to fully mature. In contrast, maturation of the MC_{TC} population does not require T cells. While both mast cell subtypes respond to activation resulting from common IgE-dependent and IgE-independent stimuli (see below), differential responses have been observed. In particular, the MC_{TC} population expresses CD88 – the receptor for complement factor C5a – and, unlike the MC_T subtype, will degranulate when challenged with C5a (Oskeritzian et al. 2005).

Functional Responses

IgE Dependent

Mast cells bind IgE immunoglobulin through high-affinity receptors, FcεRI, expressed on their cell surface. While several other hematopoietic cells also bind IgE, only mast cells and basophils do so through the unique expression of the $\alpha\beta\gamma_2$ variant. It is also important to note here that FcεRI expression on mast cells, basophils, and all FcεRI-bearing cells is very much dependent on the levels of circulating IgE. This has been decisively shown with the advent of anti-IgE therapy, which, by neutralizing IgE in vivo, prevents occupation of FcεRI by IgE and thus increases the rate by which this receptor is internalized and recycled (Macglashan 2005). Mast cells are also the only other immune cell (basophils being the other) that stores histamine within cytoplasmic granules and releases this inflammatory mediator in response to a variety of stimuli. Upon sufficient binding of allergen to specific IgE occupying FcεRI and the subsequent cross-linking of these receptors on the cell surface, a cascade of intracellular events occur leading to the rapid release (within minutes) of preformed mediators and proteases. This response, in fact, constitutes the central event in acute allergic reactions, which are also classified as type I immediate hypersensitivity reactions. During this mode of activation, cytokine generation is also initiated, with secretion typically occurring during the course of several hours. Naturally, histamine is released during

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the acute response, but several preformed proteases are as well, including tryptase, chymase, and/or carboxypeptidase A3, and proteoglycans (mostly heparin sulfate). Lipid-derived mediators are also rapidly generated de novo and released, including PGD2, LTB4, LTC4, LTD4, and LTE4. In having overlapping properties with histamine, these lipid mediators are particularly potent in inducing acute reactions. For example, if mast cell release is localized to the airways, the response is characterized by vascular leakage, contraction of airway smooth muscle, and increased mucus production. If mast cell release occurs systemically in multiple organ tissues, these mediators, along with those released as preformed substances (e.g., histamine, tryptase), can then induce full-blown anaphylaxis. Although rare, such reactions are more common in allergic individuals with hypersensitivity to food (e.g., peanut) and insect sting venom (e.g., honeybee). Increased levels of mast cell markers such as β-tryptase are sometimes detected in the plasma of subjects who have had anaphylactic reactions (see below).

IgE Independent

Mast cells also express other adaptive and innate immune receptors that are linked to activation. This is indicated above with mention that mast cells release histamine in response to C5a/C3a binding CD88. However, murine mast cells are also reported to express FcγRIII (CD16), which, if cross-linked by antigen-binding-specific IgG, has been shown to induce mediator release much like that seen during FcεRI-dependent activation (Rivera and Brugge 1995). In contrast, human mast cells have been shown to upregulate the high-affinity receptor for IgG (CD64) following in vitro exposure to IFN-γ (Woolhiser et al. 2001). Whether this has in vivo relevance is currently unknown. Studies also indicate that mast cells (both human and mouse) express several TLRs, including TLR2, TLR3, and TLR4, implying a protective role against bacteria and viruses (Varadaradjalou et al. 2003; Kulka et al. 2004). Ligands targeting these receptors (e.g., peptidoglycan (PGN) and lipopolysaccharide (LPS), respectively) induce TNF-α secretion, among other cytokines (Matsushima et al. 2004). While these non-IgE-dependent modes of activation are not likely to play a significant role in the pathogenesis of allergic disease to the extent resulting from FcεRI-mediated stimulation, they potentially do in any one of the other mast cell-mediated activities, including responses to pathogens, autoimmunity, and multiple sclerosis.

Mast Cell-Deficient Mice

Much of the current understanding of the biology of mast cells comes from studies using mast cell-deficient mice, namely, the W/W^v (W = white spotting locus) and W^{sh}/W^{sh} strains (Tsai et al. 2005). As noted above, mast cell development is dependent on SCF and its binding to the receptor protein kinase Kit (CD117), which is encoded by the proto-oncogene, c-kit. W/W^v mice have a loss-of-function mutation in c-kit, whereas the W^{sh}/W^{sh} strain occurs because of inversion mutations in upstream transcriptional regulatory elements. As a result, neither strain has mast cell precursors bearing functional CD117 and is therefore deficient in mast cells. However, because these animals produce viable SCF, it is possible to reconstitute them with bone marrow-derived mast cells (BMMC) grown in vitro from precursors obtained from genetically compatible mice. This so-called "mast cell knock-in" approach has been instrumental in deciphering the role of mast cells in many disease processes that extend beyond allergic disease and inflammation, including arthritis, multiple sclerosis, wound healing, fibrosis, and angiogenesis to mention just a few. In addition, newer models of mast-deficient mice are evolving using the Cre-Lox recombinase approach to essentially knock out specific immune cell types in mice, including the mast cell. This strategy is proving as powerful as the knock-in approach but without some of the pitfalls associated with using the W/W^v and W^{sh}/W^{sh} strains (Rodewald and Feyerabend 2012).

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Roles in Human Disease

Type I Hypersensitivity

In releasing the inflammatory mediators responsible for type I hypersensitivity reaction, mast cells (and basophils) have long been viewed as central players in the pathogenesis of allergic conditions and associated diseases such as anaphylaxis and asthma. Nonetheless, the evidence supporting this association in humans remains correlative. For example, investigators have long sought to link specific mast cell degranulation markers to anaphylactic reaction. This has certainly been attempted by looking for evidence of histamine release. However, this mediator has a very short half-life in circulation (15–60 min) and is often back down to baseline levels by the time specimens are collected following an anaphylactic reaction. Thus, it has only been useful in experimentally induced reaction such as that following bee sting-induced anaphylaxis (Eberlein-Konig et al. 1995). Moreover, its detection does not differentiate between mast cell and basophil activation. In contrast, β-tryptase is specific to mast cells and is reported elevated in plasma 1–2 h following anaphylactic reactions due to bee sting (Schwartz 1990). Interestingly, this marker is not commonly elevated following anaphylaxis due to the ingestion of foods (e.g., peanut), which has implied the involvement of basophils rather than mast cells, in reactions to oral antigens. Other mediators such as LTC4 and PGD2, like histamine, lack cell-type specificity and are thus not ideal markers of mast cell activation.

Obviously, mast cells are also implicated in the pathogenesis of human asthma. Yet again, much of the evidence in support of this belief comes from associations rather than direct confirmation as seen in the animal studies. For example, increased mast cell numbers have been identified in bronchial biopsy specimens from asthmatic subjects compared to those obtained from nonasthmatic controls (Balzar et al. 2011; Carroll et al. 2002). Careful microscopic examination of such tissue has also revealed evidence of mast cell degranulation in those specimens obtained from asthmatic individuals, which is even more prevalent in subjects who actually die from asthma (Elliot et al. 2009). Mast cell-specific markers like β-tryptase have also been detected in the bronchoalveolar lavage (BAL) fluid obtained from asthmatics compared to control subjects (Wenzel et al. 1988).

Mastocytosis

Finally, humans can develop mastocytosis, which is essentially a hyperplasia of mast cells. Several variations of the disease have been described including (1) mastocytoma, mast cell hyperplasia localized to one location; (2) cutaneous mastocytosis, mast cell hyperplasia limited to the skin and also known as urticaria pigmentosa; and (3) systemic mastocytosis – a rare condition in which the mast cell hyperplasia is evident in multiple organs such as the skin, gastrointestinal mucosa, liver, spleen, and bone marrow (Valent et al. 2012). The systemic form is often indolent and nonneoplastic, although more aggressive variants have been described often having a poorer prognosis. A somatic mutation in *a*, A816V, is commonly linked to systemic mastocytosis, which allows constitutive SCF-independent proliferation of mast cells (Akin and Metcalfe 2004). As predicted, β-tryptase levels are often elevated in this systemic form of mastocytosis. Subjects commonly experience symptoms of flushing, headache, pruritus, diarrhea, and abdominal pain resulting from nonspecific mast cell mediator release.

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Mast Cells, Growth and Development

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Synonyms

Mast cell differentiation

Definition

Growth and differentiation of a hematopoietic progenitor cell under the effects of cytokines and tissue microenvironment to give rise to mature mast cell.

Introduction

Mast cells are derived from hematopoietic progenitors. Mast cell are distinct from most other hematopoietic lineages in that their progenitors leave bone marrow as immature cells and undergo terminal differentiation in tissues where they migrate under the influence of a variety of chemokines. At least two phenotypically distinct mast cell populations can be found in tissues: (1) connective tissue or constitutive mast cells which express tryptase, chymase, and carboxypeptidase and (2) mucosal mast cells, which are found in mucosal surfaces and are recruited to the sites of inflammation such as after parasitic infections (Hallgren and Gurish 2011; Metcalfe et al. 1997). These cells expressing tryptase appear to have a more limited protease expression profile.

Growth Factor Requirements for Mast Cell Differentiation

The hematopoietic origin of mast cells was demonstrated by Kitamura et al. in 1970s by

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reconstituting the mast cells in mast cell–deficient mice (W/W^v) by bone marrow transplantation from wild type mice (Kitamura et al. 1978). Later, it was found that the mast cell deficiency in these mice was caused by defects in c-kit (Chabot et al. 1988; Geissler et al. 1988). Mice with mutations in Kit ligand (SCF) (Sl/Sl^d mice) also have similar defects in mast cell numbers (Flanagan et al. 1991; Huang et al. 1990; Williams et al. 1990; Zsebo et al. 1990). SCF is indeed the single most important growth factor for mast cell lineage development. Stem cell factor is found either cell membrane bound in bone marrow mesenchymal cells or as a soluble homodimer. It binds to its receptor Kit (encoded by c-kit). Kit is a transmembrane receptor with intrinsic tyrosine kinase activity. Its extracellular portion contains five immunoglobulin like domains which binds SCF and induces dimerization of the receptor. Upon dimerization, tyrosine kinase domain of the molecule induces autophosphorylation of the intracellular tyrosine residues creating docking sites for SH2-containing adapter molecules such as PI3 kinase, lyn, and STATs (Linnekin 1999). These signaling events create stimuli for differentiation, proliferation, and survival of mast cells. Human CD34+ progenitors cultured in SCF develop into mature mast cells in 6–8 weeks. Cytokines that positively influence SCF-induced mast cell growth and differentiation in this system include IL-6, IL-3, IL-9, IL-10, IL-15, and thrombopoietin (Metcalfe 2008). Cytokines with inhibitory effects are IL-12, GM-CSF, and TGFβ. IL-4 has a dual effect, inducing apoptosis in some systems and encouraging proliferation and maturation events including chymase and FcεR1 expression in others (Oskeritzian et al. 1999; Xia et al. 1997). Murine mast cells can also be developed in culture under the influence of IL-3. This is different than human mast cells in which IL-3 primarily yields basophils from CD34+ progenitors.

Transcription factors shown to be involved in mast cell growth and differentiation include GATA-1, GATA-2, PU-1, and MITF (Kitamura et al. 2006). MITF appears to be involved in late differentiation of mast cells while others may be involved in early differentiation events. MITF-deficient mice are also deficient in mast cells (Stechschulte et al. 1987; Stevens and Loutit 1982). MITF also cooperates with pEB-2aB1/AMLb/RUNX1 or MAZR for transcription of the mouse mast cell protease 6 (equivalent of human tryptase) (Morii et al. 2002; Ogihara et al. 1999).

Mast Cell Growth and Differentiation in Mice and Humans

Mast cell growth and development show significant differences in mice and humans. In mice, mast cells can be propagated with IL-3 from bone marrow progenitor cells even in animals deficient in SCF or Kit. In humans where SCF appears to be the major growth factor, progenitor cells cultured in IL-3 differentiate into basophils but not mast cells. There has been much debate about the origin of mast cell progenitors. In both species, mast cells progenitors leave the bone marrow and enter the blood circulation as pro-mast cells, where terminal differentiation occurs after these cells enter the tissues. In fetal mice circulation, these promastocytes were identified as Thy-1^{lo}, c-kit^{high} cells (Rodewald et al. 1996). In adult mice, some studies suggested that mast cell progenitors directly originate from a multipotential progenitor cell while others suggest they originate from a common myeloid progenitor which also gives rise to granulocytes. In experiments supporting the single lineage committed mast cell progenitors, Chen at al. showed that the progenitor population was identified as lineage negative, lacking the high affinity ▶ IgE receptor and CD27 (a marker of hematopoietic progenitors), and possessing β7 integrin (an integrin important in homing of mast cells) and IL33R (also known as T1/ST2, a cytokine receptor expressed by mast cells) (Chen et al. 2005). These cells, when cultured in a cytokine milieu supportive of multilineage myeloid development, only gave rise to mast cells, and reconstituted the mast cell compartment in mast cell deficient lethally irradiated Kit $^{W\text{-}sh}$/Kit $^{W\text{-}sh}$ mice. In these experiments, limited numbers of mast cells were also

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generated from IL-33R-granulocyte/macrophage progenitors (FcγRII/III^{high}/CD34+/β7+), which were deemed to be a contamination.

In experiments supporting a mast cell progenitor shared with other myeloid lineages, a common myeloid progenitor (CMP) giving rise to all myeloid (erythroid, megakaryocytic, granulocytic, monocytic) lineages has been isolated as a IL7Ra-/Lin-/Kit+/Sca1-/FcγRII/III^{low}/CD34^{high} cell (Akashi et al. 2000). These cells reconstituted the myeloid compartment in lethally irradiated mice. These cells also gave rise to a very low level of B-cells when cultured in vitro but not to T-cells. CMPs presumably give rise to more lineage restricted granulocytic/macrophage progenitors by upregulating FcγRII/III receptors. These cells bear a subpopulation positive for surface expression of β7 integrin in spleen, but not in peripheral blood or bone marrow, which gave rise to only basophils and mast cells in a culture medium containing myeloid growth factors and reconstituted mast cells in W/W^{v} mice (Arinobu et al. 2005). These cells also expressed Thy1 and IL33R but not FcεRI. In vitro reconstitution of basophils could not be confirmed by this model as W/W^{v} mice possess basophils, albeit in lower numbers than their wild type counterparts. In contrast to the findings of Chen et al., this study also found a low level of mast cell progeny in β7 or low cells. Mast cell progenitors with β7^{high}, FcεRI+/CD45+/CD34+/lin- phenotype have also been described in mouse lung tissue (Hallgren et al. 2007).

Taken together, these studies in mice appear to indicate that a mast cell progenitor bearing β7 integrin on its surface exists within the IL7Ra-/IL33R+/Lin-/Kit+/Sca1-/FcγRII/III^{low}/CD34^{high} population. It is unclear if this population is the only population giving rise to mast cells and whether a bipotential mast cell/basophil progenitor exists outside of the spleen of C57BL mice.

There is less known about human mast cell progenitors. As mentioned above, significant differences exist between murine and human mast cell development, including the role of IL-3 in humans not being able to support mast cell development without SCF. A progenitor cell which is Kit+/CD34+/CD13+ giving rise to mast cells and monocytes but not to basophils in culture media supplemented with myeloid cytokines culture has been described in humans (Kirshenbaum et al. 1999). In studies of patients with mastocytosis, carrying of the somatic D816V c-kit mutation was used as a marker to track mast cell progenitors shared with other lineages (Kocabas et al. 2005). Assuming that the mutation occurred randomly in hematopoietic progenitors with different commitment capacities, these studies did not suggest a shared mast cell progenitor either with basophils or monocytes.

Mastocytosis: A Disorder of Regulation of Mast Cell Numbers

The essential role of c-kit in maintaining mast cell growth and differentiation is further highlighted by its involvement in mastocytosis. Mastocytosis is the disorder characterized by clonal expansion of mast cells bearing gain-of-function mutations in c-kit receptor (Akin and Metcalfe 2004a). Kit is a receptor with intrinsic tyrosine kinase activity, which gets autophosphorylated upon binding SCF. The great majority of mutations in mastocytosis occur in intracellular tyrosine kinase domain of the Kit molecule (Akin and Metcalfe 2004b). The most common of these mutations is the D816V c-kit point mutation, although other gain-of-function mutations have also been described particularly in pediatric patients (Bodemer et al. 2010). Mast cells in mastocytosis bearing D816V c-kit mutation also express CD25 (alpha chain of IL-2 receptor) on their surface in comparison to their normal counterparts (Escribano et al. 1998). To date, no role for IL-2 has been described in pathogenic mast cell proliferation.

Patients with mastocytosis can present with a variety of clinical scenarios ranging from a common indolent and self-limiting course to those associated with more hematologic disorders and poorer prognosis (Valent et al. 2001). Patients with all forms of mastocytosis are also prone to episodic mast cell activation events including anaphylaxis, suggesting a role for c-kit mutations in activation of mast cells (Akin et al. 2010).

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In contrast to many of their other hematopoietic counterparts, a mast cell–deficient state has not been described in humans.

Cross-References

- ▶ IgE Receptor
- ▶ Mastocytosis

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Mastocytosis

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Synonyms

Urticaria pigmentosa

Definition

Mastocytosis is a clonal disease characterized by abnormal growth and accumulation of mast cells (MCs) in different tissues. The disease can be classified as cutaneous (CM), when MC infiltrate is limited to the skin, and systemic mastocytosis (SM) when MCs proliferate in other organs such as the bone marrow, gastrointestinal tract, lung, liver, spleen, or lymph-nodes.

In 1869, Nettleship and Tay described a unique cutaneous disease that showed a symmetrical spread with pigmented maculopapular lesions and an urticaria-like response to rubbing or scratching. The disease was termed urticaria pigmentosa (UP). In 1949, Ellis described a systemic form of mastocytosis with involvement of visceral organs, and in 1950, the first case of mast cell leukemia was described.

The majority of cases of mastocytosis are associated with somatic mutations of *kit*, the receptor for Stem Cell Factor. *Kit* is constitutively expressed on mature MC, and its activation leads to increased proliferation, prolonged survival, and augmented mediator release. In more than 90 % of adults with mastocytosis, an activating *kit* point mutation on exon 17 at codon 816 (substitution of aspartate by valine in the tyrosine kinase domain of the *kit* receptor or Asp-816-Val or *kit*D816V) can be detected. This mutation leads to autoactivation of the receptor, resulting in MC proliferation. All mutations were somatic and led to *kit* activation (Longley et al. 1996, 1999).

Clinical symptoms of CM and SM are mostly due to the release of MC-derived mediators (histamine, leukotriene C_4, prostaglandin D_2, *Platelet-Activating Factor*, heparin, tryptase, chymase) and/or to MC infiltration in different organs such as bone marrow, gastrointestinal tract, liver, spleen, and lymph-nodes (Escribano et al. 2002).

The European Union/US consensus group defined criteria for the classification of systemic mastocytosis in 2001 that were adopted by the World Health Organization in 2001 and 2008. The WHO classification includes seven variants of mastocytosis: cutaneous mastocytosis (CM), indolent systemic mastocytosis (ISM), systemic mastocytosis with an associated clonal

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Mastocytosis, Table 1 WHO classification of mastocytosis

Variants	Abbreviation
Cutaneous mastocytosis	CM
Maculopapular cutaneous mastocytosis[a]	
Diffuse cutaneous mastocytosis	
Cutaneous mastocytoma	
Indolent systemic mastocytosis	ISM
Smouldering systemic mastocytosis	SSM
Indolent bone marrow mastocytosis	BMM
SM with an associated hematopoietic clonal non-mast cell lineage[b]	SM-AHNMD
Aggressive systemic mastocytosis	ASM
ASM with eosinophilia[c]	
Mast cell leukemia	MCL
Mast cell sarcoma	MCS
Extracutaneous mastocytoma	

[a]*Urticaria pigmentosa*
[b]AHNMD subtype is established according to WHO
[c]In some patients, FIP1L1-PDGFRA mutation is present

hematologic non-mast cell lineage disease (SM-AHNMD), aggressive systemic mastocytosis (ASM), mast cell leukemia (MCL), mast cell sarcoma (MCS), and extracutaneous mastocytomas (Table 1) (Valent et al. 2001, 2003).

Mastocytosis includes a wide spectrum of clinical entities, ranging from skin-limited disease to variants characterized by hematological involvement and a worse prognosis (Austen 1992; Tefferi and Pardanani 2004).

Cutaneous mastocytosis is defined as an accumulation of mast cells limited to the skin. The most common skin manifestation in both children and adults (CM or SM) is *urticaria pigmentosa* also defined as maculopapular cutaneous mastocytosis and characterized by brown or red-brown maculae and papules (in adults <0.5 cm, usually larger in children) that can increase in volume and develop a wheal-and-flare reaction when scratched (Darier 's sign) (Hartmann and Henz 2002).

Diffuse cutaneous mastocytosis (DCM) is a form of CM characterized by a diffuse mast cell infiltration in the dermis. Solitary mastocytoma (MAST), sometimes with blistering, occurs predominantly in childhood (before 3 months) and in most cases resolves spontaneously. Much rare are the bullous variant (often in the first weeks of life), the plaque form, the nodular form as well as *telangiectasia macularis eruptiva perstans* (TMEP) with multiple hyperpigmented maculae as well as erythema and telangiectasia (Brockow 2004).

The diagnosis of CM is based on the presence of typical skin lesions (major criteria) and almost one of the following minor criteria: (1) multifocal mast cell infiltrates in the skin biopsy or (2) activating *kit* point mutations (most often *kit*D816V). In all adult patients with skin lesions, SM must be excluded by bone marrow biopsy. CM usually has a good prognosis, with substantial improvement or spontaneous resolution before puberty. In a few cases (<10 %), particularly in diffuse cutaneous form, skin lesions can persists in adults. In these cases, the disease may remain active through adolescence and persist as systemic adult mastocytosis. In contrast to childhood-onset mastocytosis, skin lesions in adult usually persist or increase through lifetime. In patients with ASM or MCL, cutaneous lesions are often absent.

Systemic mastocytosis is characterized by an increase in mast cells in the skin and in extracutaneous organs such as bone marrow, gastrointestinal tract, lymph-nodes, liver, and spleen. Clinical picture is usually the result of local and systemic mast cell mediator release or of mast cell proliferation and infiltration in different organs with consequent organomegaly and eventually progressive loss of the organ functions.

Typical clinical findings that would point to the presence of SM include headache attacks, flushing, often in combination with hypotension, syncope and tachycardia, gastrointestinal complaints (nausea, burning abdominal pain, cramp-like colics, often episodes of diarrhea, vomiting, gastritis, peptic ulcers), rhinitis, acute dyspnea, dysequilibrium, fatigue, musculoskeletal pain, and depression (Jensen 2000; Castells and Austen 2002; Haeberli et al. 2003). Approximately 10–30 % of patients with mastocytosis develop osteopenia or osteoporosis with bone pain and pathological fractures (Austen 1992). Anaphylactic reactions have been reported in all forms of mastocytosis (Escribano et al. 2002;

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Mastocytosis, Table 2 B and C findings in systemic mastocytosis

B findings	C findings: organ dysfunction[a]	Progressive C findings
1. Mast cell infiltration:	–	–
Mast cell infiltration in bone marrow >30 %		
Serum tryptase > 200 ng/ml		
2. Myelopoiesis alteration:	1. Marrow dysfunction cytopenia:	Severe pancytopenia
Hypercellular marrow with fat cell loss or with mild dysplasia or myeloproliferation, normal or mild alteration of blood count without progression	Neutrophils <1,000/μl	Neutrophils < 500/μl + Recurrent infections
	Hb < 10 g/dl	Necessity of transfusions
	Ptl < 100,000/μl (One or more alteration)	Ptl < 20,000/μl, recurrent bleeding
3. Organomegaly:	2. Hepatic dysfunction:	Progressive decrease of hepatic function, coagulation abnormalities
Hepatomegaly	Hepatopathy with ascites or portal hypertension	
Lymphoadenomegaly: visceral lymph-nodes > 2 cm		
Splenomegaly without hypersplenism	3. Spleen dysfunction:	–
	Splenomegaly with hypersplenism	
	4. Gastrointestinal dysfunction:	–
	Malabsorption with weight loss	
	5. Bone alteration:	–
	Osteolysis – pathological bone fractures	

[a]C findings: organ dysfunction is due to mast cells infiltration

Tefferi and Pardanani 2004); wasp or bee stings are the most common triggers of acute reactions (Haeberli et al. 2003; Brockow et al. 2008). Coagulation abnormalities and bleeding diathesis, in particular in the gastrointestinal tract, may be due to heparin mast cells release.

Clinical symptoms due to mast cells infiltration are classified into B and C findings (Table 2). B findings are the result of a mast cell infiltration without organ dysfunction. In contrast, C findings are the result of a clinically relevant impairment or loss of organ function and represents an indication for cytoreductive treatment.

For the diagnosis of systemic mastocytosis, according to the WHO, SM criteria should be fulfilled (Table 3). The diagnosis is suspected in patients with recurrent episodes of *flushing*, pruritus, headache, gastrointestinal symptoms (nausea, burning abdominal pain, diarrhea, vomiting, gastritis, peptic ulcers), frequent episodes of hypotension, anaphylactic reactions (e.g., after hymenoptera stings), and bone abnormalities (osteoporosis, bone fractures).

Mastocytosis, Table 3 SM criteria

Major criterion[a]	Multifocal dense infiltrates of mast cells (>15 mast cells in aggregates) in bone marrow biopsies and/or in sections of other extracutaneous organ(s)
Minor criteria[a]	(a) >25 % of all mast cells are typical cells (type 1 or type II) on bone marrow smears or are spindle shaped in mast cell infiltrates detected on section of visceral organs
	(b) c-kit point mutation at codon 816[b] in the bone marrow or another extracutaneous organ
	(c) Mast cell in bone marrow or blood or another extracutaneous organ expresses CD2 and/or CD25
	(d) Baseline serum tryptase concentration >20 ng/ml (in the case of unrelated myeloid neoplasm, (d) is not valid as SM criterion)

[a]One major criterion plus one minor criterion or three minor criterion occur for SM diagnosis
[b]In the majority of cases: Asp816→Val (D816V)

When SM is suspected, a first important step is the evaluation of the serum tryptase level. Mast cell tryptase is the most widely used surrogate disease marker in mastocytosis (Schwartz et al. 1995;

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Sperr et al. 2002). Beta-tryptase is stored in mast cell granules, while alpha-tryptase is believed to be secreted constitutively from the cells. The mean total tryptase level in a healthy population is approximately 5 ng/ml (Valent et al. 2004). A level greater than 12 ng/ml, particularly if persisting on two or more determinations, is suggestive of mastocytosis. Tryptase is normal (<12 ng/ml) in most patients with CM but is almost invariably elevated in those with SM. An important aspect is that tryptase levels increase (transiently) during significant mast cell activation that may, for example, occur during a systemic allergic reaction. In such cases, it is recommended to repeat the test a few weeks later. If the tryptase level is persistently elevated, SM should be considered as an underlying disease and a bone marrow biopsy is required to confirm diagnosis.

Moreover, tryptase levels reflect the total burden of mast cell in SM and correlate with mast cell infiltration in the bone marrow (Sperr et al. 2002). However, a persistently elevated serum tryptase levels are also found in myeloid leukemia and in other myelodysplastic disorders in the absence of SM (Valent et al. 2004).

The prognosis differs for each category of systemic mastocytosis. Several variables are associated with a poor survival such as the presence of hematological abnormalities and organ dysfunction (C findings). Patients with ISM have in general a good prognosis. ASM and MCL have a severe prognosis with a survival time that depends from the response to an aggressive management (Valent et al. 2003; Tefferi and Pardanani 2004).

A principal objective of treatment in all categories of mastocytosis is the control of mast cell mediator–induced signs and symptoms. A standard treatment for mastocytosis is difficult to apply to individual patients based on the variable clinical course (Valent et al. 2007). A general consensus for using anti-mediator agents such as antihistamines, cromoglycate sodium, ketotifen, and antileukotrienes is recommended. These agents can be introduced based on the clinical course of the patient. Many patients require a combination of anti-H1 and anti-H2 antihistamines. Second-generation antihistamines such as desloratadine, fexofenadine, levocetirizine, or rupatadine may be used to treat symptoms of mastocytosis. Psoralens and ultraviolet-A (P-UVA) or corticosteroids can be used to reduce pruritus and whealing (Valent et al. 2007).

Cytoreductive treatment is limited to aggressive forms with C findings. Various chemotherapy regimens have been used in the treatment of systemic mastocytosis. Interferon-alfa and 2-chlorodeoxyadenosine (Cladribine) have reached benefits in approximately 60 % of patients (Kluin-Nelemans et al. 1992; Tefferi et al. 2001). The tyrosine kinase inhibitor imatinib mesylate may be useful in those types of systemic mastocytosis (systemic mast cell disease) that do not have mutations of the codon 816 on the c-*kit* gene and carry the wild-type *kit* (Akin et al. 2003). Imatinib mesylate may also be useful in a subtype of systemic mastocytosis that carries the *FIP1L1-PDGFRA* rearrangement. Other tyrosine kinases such as dasatinib and masatinib and a protein kinase C inhibitor (midostaurine) are currently under investigation for the treatment of aggressive mastocytosis.

Cross-References

- ▶ Mast Cell Mediators
- ▶ Mast Cells, Growth and Development

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Methacholine Challenge

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Definition

Methacholine challenge is a form of direct bronchial challenge that is commonly used in the diagnosis of asthma.

Essay

Methacholine challenge is a form of direct bronchial challenge used in the diagnosis of asthma. A direct challenge is one that acts directly on the airway smooth muscle, mucus glands, and/or microvasculature to cause bronchoconstriction. Direct versus indirect bronchial challenges are discussed further in the separate entry entitled: *Bronchial Challenges*. Methacholine challenge is the most commonly used type of bronchial challenge, likely because it is readily available and has been studied extensively in the literature. The details of its methodology have been examined closely, and there is an abundance of data validating its use as a method of assessing Airway hyperresponsiveness (AHR) (Crapo et al. 2000). Methacholine is a muscarinic analogue that acts directly on the muscarinic receptors located on airway smooth muscle. The first muscarinic analogue to be used for bronchial provocation was acetylcholine, in 1940.

To perform a methacholine challenge, one must first ensure that an individual does not show excessive variability from one spirometry to the next and that he/she do not show AHR to placebo, which consists of the same normal saline used as part of the nebulizer solution to deliver methacholine during the challenge. Once the patient demonstrates reproducible efforts following inhalation of placebo solution, the FEV1 from

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these efforts is considered his/her baseline. At this point, incremental doses of methacholine are administered by nebulizer, starting at 0.03 mg/mL and doubling the concentration with each subsequent dose until a final concentration of 16 or 32 mg/mL (Cockcroft 2008). A spirometry is performed immediately following each dose in order to look for a drop in FEV1 from baseline. Once the FEV1 decreases by 20 % or more from baseline, the test is stopped and the patient is given a bronchodilator to reverse the bronchoconstriction elicited by the test and to reverse any symptoms that might have developed as a result of the test.

The two most common methods of performing a methacholine challenge, the 2-min tidal breathing method and the five (total lung capacity)-breath dosimeter method, vary mainly in their methods of aerosol generation and inhalation. More specifically, the dosimeter method administers only about half of the total aerosol at each concentration and does so in a breath-activated manner rather than a continuous one. Although these methods were previously thought to be equivalent, more recent studies suggest that the dosimeter method can yield more false negatives due to bronchoprotection provided by taking deep inhalations to total lung capacity and then holding one's breath, particularly in the group with very mild AHR. As such, recent recommendations suggest using the 2-min tidal breathing method or a modification of the dosimeter method that does not involve breathing to TLC. (Cockcroft 2008; Cockcroft et al. 2005; Cockcroft and Davis 2006)

The dose of methacholine that results in a 20 % drop in FEV1 is called the PC_{20} (or PD_{20}) and is considered a measure of AHR. Different guidelines vary with regard to what PC_{20} is considered abnormal and therefore indicative of AHR. The American Thoracic Society (ATS), for example, considers a threshold PC_{20} of 16 mg/mL as "positive" (Crapo et al. 2000), whereas many research studies use a threshold of 8 mg/mL. In addition to a cutoff for normal versus abnormal, the ATS guidelines arbitrarily identified the following severities of AHR: $PC_{20} < 0.25$ mg/mL as marked AHR, PC_{20} of 0.25–1 mg/mL as moderate AHR, PC_{20} of 1–4 mg/mL as mild AHR, and PC_{20} of 4–16 mg/mL as borderline AHR (Crapo et al. 2000). Ultimately, however, AHR is variable and can be affected by differences in inflammatory stimuli, as well as certain medications and overall disease control. In addition, one must use caution not to equate severity of AHR with severity of asthma since the two do not necessarily correlate with one another (Cockcroft 2008). The results of a methacholine challenge should be interpreted with these factors in mind and should always be taken in clinical context.

Since many asthmatics are evaluated with bronchial challenges after therapy with anti-inflammatory medications or those with bronchodilator effects, it is important to recognize that these medications can alter the PC_{20} of a methacholine challenge and presumably also the results of other challenges. Because of this, it is important for patients to hold certain medications prior to having such a challenge performed. Short-acting beta-agonists, such as albuterol, should be held for 8 h prior to a methacholine challenge, whereas the medium-acting bronchodilator iptratropium should be held for 24 h leading up to the test. Long-acting beta-agonists, such as salmeterol and formoterol, and the long-acting anticholinergic tiotropium should be held for a full 48 h prior to testing. Patients should hold theophylline for 12–48 h, depending on the preparation, and leukotriene modifiers should be held for 24 h. The effect of antihistamines is variable, so they should be held for 24–72 h depending on how long their effect is supposed to last (Crapo et al. 2000). Caffeinated beverages can also affect bronchial hyperresponsiveness in a manner similar to theophylline and should therefore be held on the day of a challenge (Henderson et al. 1993). Although they usually do so to a lesser degree, inhaled and systemic corticosteroids can also impact methacholine challenges by reducing AHR by a magnitude of 1.5–6 doubling dose. This results in a higher dose of methacholine needed to induce a 20 % drop in FEV1, yielding a higher PC_{20} (Ward et al. 2002; van den Berge et al. 2001; Juniper et al. 1990; Kerrebijn et al. 1987).

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For a discussion of contraindications to methacholine challenges, please see the separate entry entitled: *Bronchial Challenges*. For a comparison of methacholine challenge and mannitol challenge, please see the separate entry entitled: *Mannitol Challenge*.

Cross-References

- ▶ Bronchial Challenges
- ▶ Mannitol Challenge

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Methods (In Vitro and In Vivo): Multiplex Immunoassay Systems

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Synonyms

ISAC; Luminex; Microarray

Definition

Multiplex immunoassays are procedures used in laboratories to detect and quantify analytes (antigens or antibodies) with multiple specificities in one reaction well or assay analysis. They involve the manual or computer-automated mixing of multiple antigen and antibody reagents together in one reaction vessel to permit immune-complex formation and ultimately generation of multiple isotopic, colorimetric, fluorescent, or chemiluminescent response signals. The measured responses are either proportional (noncompetitive binding) or inversely proportional (competitive binding) to an analyte's concentration following interpolation from a reference curve. This section will use IgE antibody and indoor aeroallergens as model analytes for illustration of the current multiplex technology.

Introduction

The first single-plex immunoassay was reported for the measurement of human insulin (Berson and Yalow 2006) (see ▶ Single-Plex Immunoassays and Autoanalyzers). This assay involved a competitive binding reaction in a series of test tubes containing radiolabeled and unlabeled

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insulin for limited insulin-specific IgG antibody binding sites. One human serum specimen could be analyzed in one duplicate set of test tubes. Shortly thereafter, the first IgE antibody test based on the immunoassay principles put forth by Berson and Yalow was reported as the radioallergosorbent test (Wide et al. 1967). It employed a paper disc to which allergen extracts were coupled to bind antibody in a noncompetitive reaction. Following a buffer wash bound IgE was detected with a radiolabeled anti-IgE, and the resultant final radioactivity resident on the disc was proportional to the quantity of IgE antibody in the original test serum. Again, this was a single-plex assay in that one serum could be evaluated for the presence of IgE antibody to one allergen specificity in each of the reaction tubes.

From these early immunoassay formats, many non-isotopic single-plex assay variations have been developed and commercialized over the years (Matsson et al. 2008; Hamilton 2010). However, there has always been the goal of developing new assay formats that provide more rapid turnaround times with automation and that they use smaller quantities of specimen. In general, this has not been possible without a loss in analytical sensitivity and specificity and assay performance (see ► Assay Performance Parameters). Development of rapid point of care assays attempted to address part of this goal which was the use of small quantities of serum with a rapid turnaround time. However, these lateral flow immunoassays have not been able to match the performance of autoanalyzer-based single-plex assays in terms of their analytical sensitivity and the ability to quantify the level of analyte in a specimen. The emergence of multiplex assay technology in the diagnostic allergy field using recombinant and native component allergens and panels of antisera specific for indoor aeroallergens has begun to meet this challenge.

Allergen Components

Allergen extracts by their nature are complex mixtures of many proteins, lipoproteins, and glycoproteins, some of which are allergens that elicit IgE antibody in genetically predisposed hosts. Using foods as an illustration, it is noteworthy that of the several hundred foods that are known to contain allergens and elicit food allergy symptoms, only a small number (chicken egg, cow's milk, peanut, soybean, wheat, tree nuts, and fish) elicit the majority of food-induced allergic reactions (Sicherer 2001; Breiteneder and Ebner 2000). For some of the clinically most important allergenic food specificities, the principal allergenic components have been identified, cloned, sequenced, and generated as recombinant proteins (Vieths et al. 1998). Some recombinant allergens that are poorly immunoreactive with IgE antibody as a result of not maintaining their antigenic epitopes can be replaced with native molecules that are purified directly from food extracts. Some allergenic proteins with analogous structures and biological functions in different species of plants can be recognized by the same IgE antibody, even though there has been no known exposure to that allergen specificity. This binding is described as cross-reactivity across structurally similar molecules.

Peanut is the one allergenic food where component-specific IgE testing has been shown to provide diagnostically useful information for selecting individuals who are candidates for oral food challenges. Component-resolved diagnostics using both single-plex and chip-based multiplex microarray analysis (see below) was used to successfully discriminate between children who were IgE anti-peanut positive and failed the food challenge from those who passed the challenge and were thus deemed to be peanut tolerant (Nicolaou et al. 2010). These investigators observed that nearly one quarter of IgE anti-peanut-extract-positive (sensitized) children failed an oral peanut challenge. In this cohort, the group 2 peanut allergen (Ara h 2) was the IgE anti-peanut component specificity that best predicted a failed oral peanut challenge. Other investigators have confirmed that Ara h 2, sometimes together with Ara h 1- and 3-specific IgE antibody, can effectively differentiate between peanut-allergic and peanut-tolerant children

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(Dang et al. 2012; Pedrosa et al. 2012; Ebisawa et al. 2012). In contrast, the group 8 allergen in peanut (Ara h 8) is structurally similar to and thus cross-reactive with group 1 aeroallergen from birch pollen (PR-10/Bet v 1 homologue family). Exclusive IgE anti-Ara h 8 positivity in an absence of IgE anti-Ara h 1, 2, and 3 reflects an individual who tends to experience only mild allergic symptoms restricted to the oral cavity following exposure to peanut (Asarnoj et al. 2012). At present, peanut appears to be the unique food where component-resolved IgE antibody testing is known to provide enhanced diagnostic information over the peanut extract-based food-specific IgE measurement.

Multiplex Immunoassays for Antigens and Antibodies

A multiplex assay is a procedure by which analytes of multiple specificities are detected and, in some cases, quantified in a single specimen using a single reaction mixture of reagents. In the context of diagnostic allergy testing, a multiplex assay can measure IgE antibody to multiple allergen specificities in a single reaction vessel. One excellent illustration of this assay format is the immunosorbent allergen chip test (ISAC) microarray in which more than 100 individual purified allergens (often recombinant in nature) are adsorbed onto triplicate spots on a silicon microchip (Jahn-Schmid et al. 2003). A small quantity of serum is then applied to the microchip during which time antibody if present will bind to any of the more than 100 individual allergens on the chip surface. Following a buffer wash to remove unbound serum proteins, bound IgE is then detected with antihuman IgE conjugate and a subsequent addition of substrate. Both species-specific allergenic components and food-aeroallergen cross-reactive allergenic specificities including the PR-10/Bet v 1 homologue, lipid transfer protein, and tropomyosin and profilin allergen families are present on the ISAC chip. An analogous but less well-documented chip-based microarray for IgE antibody detection has been reported that uses allergen extracts instead of allergenic components (Dottorini et al. 2011). This latter assay's performance against established predicate devices requires further documentation before its performance is known. In North America, data from these chip-based IgE assays are considered only supplemental support to diagnostic autoanalyzer-based single-plex IgE antibody results (see ▶ Single-Plex Immunoassays and Autoanalyzers) because they are not currently cleared for use in clinical testing by the US Food and Drug Administration.

An alternative multiplexing system involves the xMAP® technology (Luminex Corp., Austin, TX) in which polystyrene microspheres are internally labeled with a panel of fluorophors to create distinct sets of microspheres that can be distinguished from each other when they pass through laser beam in a fluid flow cell. The surface of separate bead sets is subsequently covalently coupled with different allergen-specific monoclonal antibodies. This enables beads with different internal fluorophors and each set having a unique monoclonal capture antibody for a different indoor aeroallergen to simultaneous capture and detect multiple allergens in a single extract of household dust (Earle et al. 2007). The multiplex array for indoor allergens (MARIA), in its current configuration, is an 8-plex which allows simultaneous detection of allergens of dust mite (Der p 1, Der f 1, Mite Group 2), cat (Fel d 1), dog (Can f 1), mouse (Mus m 1), rat (Rat n 1), and German cockroach (Bla g 2). A modification of the MARIA to detect IgE antibody to multiple indoor aeroallergen specificities that uses allergens coupled to different microbead arrays has been recently reported (King et al. 2013).

Summary

Immunoassay technology has evolved from individual "single-plex" testing in which one analyte is measured in a single reaction cell to multiplexing in which multiple antigens or antibodies are detected in the same immune reaction cell. The result is a reduction in the volume requirements for specimen and a more rapid turnaround time. In the area of diagnostic allergy testing, multiplex assays are available to

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simultaneously detect IgE to multiple allergen specificities and to quantify multiple indoor allergens in an extract of surface "reservoir" house dust.

Cross-References

- Analytes and Biomarkers: IgE
- Assay Performance Parameters
- Cow's Milk Allergy
- Diagnostic Assay Components
- Egg Allergy
- Food Allergies, Diagnostic Testing
- Food Allergy, Overview
- IgE Testing
- Imported Fire Ant Allergy
- Peanut Allergy

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Methods (In Vitro and In Vivo): Nephelometry and Turbidimetry

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Synonyms

Immune complex detection; Light scatter

Definition

Nephelometry and turbidimetry are analytical methods that involve instruments that detect the quantity of suspended particulate in a liquid or gas by measuring the magnitude of light beam scatter at different angles.

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Introduction

Quantification of the concentration of analytes such as immunoglobulins (IgG, IgA, and IgM) and other proteins (amyloid) in human serum is commonly performed in the clinical immunology laboratory nephelometry or turbidimetry (Karamehic et al. 2012; Wang et al. 2012). Nephelometry and turbidimetry are analytical techniques that are based on the principle of the scattering of light by a solution containing dispersed particulate matter. When light is directed through a transparent medium containing solid particles, part of the light is scattered in all directions which gives a turbid appearance to the particulate mixture. The amount of decrease of the incident light related to scattering by particles in the solution is the fundamental principle upon which turbidimetry and nephelometry are based. The difference in the two systems is that nephelometry measures the amount of scattered light at a 90°angle, while turbidimetry measures the intensity of light that is transmitted directly through the sample.

Nephelometry Versus Turbidimetry

In a nephelometer, an analyte such as human IgG binds to the analyte-specific antiserum (antihuman IgG) that is simultaneously or sequentially introduced into a reaction cuvette. Immune complexes form that cause the light incident on the reaction cell to scatter. As the concentration of the analyte increases, the amount or rate of immune complex formation increases in proportion. The amount of light scatter measured is proportional to the concentration of the analyte in the test specimen. The larger the size of the particle or immune complex, the more the scattering of light occurs. The extent of scatter produced by the amount of analyte in an unknown specimen can be directly compared to the level of scatter produced by a differing amount of the same analyte in a reference preparation.

Two strategies have been used to collect nephelometry data. In "end point nephelometry," the antibody–antigen interactions are permitted to reach completion or maximal immune complex formation before the extent of scatter is measured. Alternatively, in "kinetic nephelometry," the rate of change in scatter can be measured right after the antibody is added to the reaction vessel containing the antigen. Both strategies successfully generate dose–response curves from which unknown light scatter data can be interpolated into analyte concentrations (van Toorenenbergen et al. 2010). The use of enhanced reagent antibodies coupled to microparticles can lower the analytical sensitivity of the nephelometer into the nanogram to low microgram per milliliter range which is often needed for the quantification of human IgG4 and other analytes in low concentration such as human IgE.

Turbidimetry is considered by laboratorians to be a more reliable measure of light scatter than nephelometry when the amount of light scattering is extensive. Large amounts of light scatter occur when there are a large number of particles. When the particulate concentration is low and thus the extent of light scatter is small, nephelometry is preferred. The variables that influence the extent of nephelometry and turbidimetry performance include the intensity of the light incident on the reaction cell, the amount of scattered light that depends upon the number of particles, their size and shape of the particles or immune complexes, and the wavelength of the light used in the instrument.

Applications

Knowlton et al. (2012) compared the performance of immunoturbidimetric procedures with electroimmunoassays and immunoprecipitation-based assays to measure apolipoprotein-defined lipoprotein abnormalities in rheumatoid arthritis patients and healthy controls. They measured apolipoprotein and lipoprotein profiles in the serum of 94 patients with rheumatoid arthritis and 79 controls using the 3 assay methods. The rheumatoid arthritis patients had significantly higher levels of total cholesterol triglycerides and very-low-density lipoprotein cholesterol than controls using all three assay methods. In addition, significantly lower levels of

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apolipoprotein and lipoprotein (Lp) A-I:A-II, but not LpA-I, were observed in the serum of rheumatoid arthritis patients. The study nicely demonstrates the utility of turbidimetry in the quantification of lipoproteins in human serum.

The utility of turbidimetry as a rapid screening tool was demonstrated by Sekiya et al. (2012). The group used a turbidimetric measurement of a solution of collagen, heparin, and test compound in a high-throughput format to identify heparin-neutralizing agents and low molecular weight heparin mimetics. Collagen is known to spontaneously form insoluble fibrils when it is transferred to a physiological buffer. Using the knowledge that this process is inhibited by heparin, they screened a chemical library of 34,400 compounds for heparin-neutralizing capacity. Their assay was based on the principle that the presence of a heparin-neutralizing agent or a heparin mimetic would prevent collagen forming fibrils, thus reducing turbidity. Using this assay, the group was able to identify a novel heparin-neutralizing agent. They concluded that this compound screening assay protocol is most feasible for an automated high-throughput screening (HTS) system.

In addition to measuring analytes such as apolipoprotein and other human proteins such as IgG, IgM, IgA, and amyloid, nephelometry and turbidimetry are also being used to evaluate general air quality for assessing the extent of air pollution, monitoring the change in climate parameters, and determining the extent of visibility on any given day where smog is expected. There are a number of biological contaminants that produce light scatter. These include airborne fungal particles, bacteria, viruses, animal dander, dust mites, pollen, and human skin cells. Finally, nephelometers with three wavelengths are being used in global warming studies to assess the amount of solar radiation that is reflected back into space as a result of dust and particulate matter. They are also being used to study seasonal variability in physical and chemical fluxes and suspended particular matter in estuaries (Uncles et al. 2000). During a year period of observation, turbidity was shown in a reference estuary to be low, with low levels of suspended chlorophyll (typically <2 µg/l) as a result of tidal water exchange with the adjoining bay.

Summary

The nephelometer and turbidimeter are laboratory instruments that quantitatively detect the extent of light scatter as a result of particulate or immune complex formation between antigens and antibodies in a reaction cell. Their principal application in the clinical immunology laboratory is to quantify human serum proteins; however, they both have other applications in the assessment of particulate in the air as a result of pollution, the monitoring of climate change with changes in atmospheric and water particulates, and the extent of smog and visibility.

Cross-References

- ▶ Analytes and Biomarkers: IgE
- ▶ Analytes and Biomarkers: Precipitin Antibodies

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Methods (In Vivo) Provocation Tests (Nasal Challenge, Bronchial Challenge, Food Challenge)

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Synonyms

Bronchial challenge test; Conjunctival challenge test; Food challenge test; Nasal challenge test

Definition

In terms of allergy diagnosis, provocation tests involve direct allergen challenge to end organs (nasal or bronchial passages, conjunctiva, and gastrointestinal tract) for the purpose of verifying that a sensitized (IgE antibody-positive) individual is truly allergic, as manifested by objectively identified allergic symptoms. Nasal, bronchial, conjunctival, and food challenge tests are considered reference diagnostic methods in the diagnostic algorithm of allergic disease.

Introduction

The diagnosis of human allergic disease begins with a detailed clinical history and physical examination, during which the clinician identifies a relationship between a reported allergic symptom and an allergen exposure (Bernstein et al. 2008). This raises a suspicion of the presence of allergic disease which is then followed by confirmation of sensitization (IgE antibody positivity). The primary confirmatory tests for allergic sensitization involve detecting IgE antibody in the skin [see ▶ Methods (In Vivo): Skin Test (Intradermal, Puncture)] and/or the blood (see ▶ Single-Plex Immunoassays and Autoanalyzers] (Matsson et al. 2008). Skin and serological tests for IgE antibody provide information about the allergen specificity and state of an individual's sensitization. However, the presence of IgE antibody in the skin or blood does not in itself verify that the individual is allergic without the linkage to objectively observed clinical symptoms.

When there is discordance between the results of a clinical history and these primary confirmatory skin and blood tests, a third level of diagnostic testing is considered which involves allergen provocation of an end organ. The direct provocation of an end organ (nasal or bronchial passages, conjunctival, gastrointestinal tract) is often considered the most definitive test for the presence of allergic disease. However, provocation tests are time-consuming, more expensive than skin or serological tests, and often complicated to perform and interpret in a reproducible manner, and they can be potentially hazardous as they involve direct exposure of the individual to the suspected allergen and observation for an allergic symptom. While the skin test is a form of in vivo provocation that is localized to a restricted area of skin, skin testing will not be discussed in this overview as it is examined in detail elsewhere [see ▶ Methods (In Vivo): Skin Test (Intradermal, Puncture)]. Rather, this overview will examine the provocation of the nasal passages, bronchi, conjunctiva, and gastrointestinal tract. Reactions to airborne allergens can be confirmed using a nasal, bronchial, or conjunctival challenge test. Food allergen-induced allergic reactions can be verified with a food challenge.

Nasal Provocation Test

Direct exposure of the nasal mucosa to allergen is primarily considered a research tool that is used in the verification of allergic rhinitis. Occasionally, it is used in the clinic for the diagnosis of allergic and occupational rhinitis (Rajakulasingam 2003). The first administration into one or both nostrils with a metered dose delivery device is the diluent solution alone

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with no allergen. This detects any nonspecific responses that might occur due to irritation. During the next 15 min following the administration, the number of sneezes is quantified, and the quantity of nasal discharges is measured. A number of symptoms including pruritus, rhinorrhea, nasal blockage, and ocular discharge are also recorded. If diluent also induces no clinically observed or patient reported symptoms or significant changes on a rhinomanometer, then the provocation is continued by adding allergen to the diluent and introducing it into the nose. The patient holds his or her breath during each allergen administration to avoid inhaling the allergen into the airways. Every 15 min, the dose of allergen is increased until symptoms are detected. In research studies, the nasal discharge that is collected either directly or following a nasal lavage can be evaluated in vitro for mast cell mediators such as histamine and TAME esterase (see ▶ Mast Cell Mediators). Nasal airway resistance is not generally used as an end point for nasal challenge monitoring as it tends to be highly variable (Scadding et al. 2012).

Bronchial Provocation Test

The detection of IgE antibody in the skin or blood is generally effective in identifying an allergy to an inhaled substance, and thus, a bronchial provocation challenge with allergen is considered principally a research procedure. There are special cases such as in the investigation of occupational asthma when the skin or blood test results are negative and where a bronchial challenge may be useful to confirm an allergy. Possibly, the most widely used bronchoprovocation procedure used clinically involves the administration of methacholine for the diagnosis of difficult cases of asthma. The methacholine challenge is discussed in detail elsewhere [see ▶ Methods (In Vivo): Methacholine Challenge]. In brief, either methacholine or histamine is inhaled using a calibrated nebulizer, starting at doses of 0.05–0.1 mg/mL and doubling the concentration up to 10–25 mg/mL. In selected cases, allergen extracts are administered in a similar manner with increasing doses. Pulmonary function is monitored after each dose using a spirometer. A positive response is usually defined as the concentration of agonist (methacholine or allergen) that induces a drop in the forced expiratory volume per second (FEV1) of 20 % or more from the baseline (Fish and Peters 2003; Katial and Covar 2012).

Conjunctival Provocation Test

For individuals in whom allergic responses are selectively manifested in the eyes, a conjunctival provocation test may be useful during clinical evaluation. Otherwise, like the nasal and bronchial challenge, the conjunctival provocation test is most commonly used as a research tool for studying changes in ocular sensitivity following an intervention (Dreborg et al. 2012). The conjunctival provocation involves an initial administration of a drop of diluent solution into one conjunctival sac. This first step identifies any nonspecific responses that might occur due to irritation. If no eye or nose allergy symptoms are recorded during the 15-min period following diluent administration, then allergen in the same diluent is administered onto the conjunctiva. As with the bronchial challenge, the dose of allergen is then increased every 15 min until allergic symptoms are detected. The concentration of allergen in the solution that elicits an allergic response provides a relative indication of the degree of the patient's sensitivity to the allergen (Irkec and Bozkurt 2012).

Food Challenge Test

Symptoms of mouth itching or swelling, itchy rash, wheezing, and vomiting shortly after consuming a particular food indicate a possible food allergy. Confirmation of sensitization to a particular food with food-specific IgE antibody by skin testing or serology is not perfect as both false-positive and false-negative test results occur. Thus, the most definitive test for documenting food allergy is a food challenge in which an allergic reaction is observed following to controlled

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consumption of the suspected food. There are many approaches to the performance of a food challenge test (Pongracic et al. 2012). Under careful supervision, some clinics will first wipe the food across the patient's lower lip and observe for 20 min for any signs of redness, itching, swelling, or eye or nose symptoms. If not, a small amount of the food is introduced into the mouth. The double-blind placebo-controlled food challenge (DBPCFC) is considered the definitive diagnostic test for food allergy. Open- and single-blinded food challenges are more commonly used in clinical practice. Gradually, the amount of food consumed is increased if no symptoms are observed at 20 min. If no reaction is observed following a cumulative dose that is equivalent to a normal daily portion, then the patient may return home and observe himself/herself for any delayed reaction during the following 24 h (Järvinen and Sicherer 2012).

The oral food challenge has been used to identify serological levels of IgE antibody that may identify patients at high risk for food allergic reactions. Sampson performed a prospective study of children and adolescents who had been evaluated by skin test double-blind placebo-controlled food challenge and serology for food-specific IgE antibody (Sampson 2001). Levels of IgE antibody for egg, milk, peanut, and fish were identified, above which they could predict clinical reactivity based on a positive food challenge with more than 95 % certainty. This work began the use of food-specific IgE antibody to identify a subset of children who were highly likely (>95 % probability) to experience a clinical reaction to egg, milk, peanut, or fish. The judicious use of quantitative food-specific IgE antibody measurements is now used in the identification of select patients in whom a time-consuming oral food challenge may not be necessary.

Summary

Provocation challenge involving the administration of allergen into the nose, lungs, conjunctiva, and gastrointestinal tract is considered a definitive diagnostic reference method for identifying individuals who are allergic. For aeroallergens, nasal, bronchial, and conjunctival provocation challenges remain primarily research tools. In contrast, food provocation tests are considered the reference method for food allergy diagnosis, and they are used in clinics for definitive determination of food allergy.

Cross-References

- ▶ Cow's Milk Allergy
- ▶ Egg Allergy
- ▶ Food Allergies, Diagnostic Testing
- ▶ Food Allergy, Overview
- ▶ IgE Testing
- ▶ Imported Fire Ant Allergy
- ▶ Mast Cell Mediators
- ▶ Methods (In Vivo): Skin Test (Intradermal, Puncture)
- ▶ Peanut Allergy
- ▶ Single-Plex Immunoassays and Autoanalyzers

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Methods (In Vivo): Methacholine Challenge

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Synonyms

Direct challenge test; Methacholine inhalation test

Definition

A methacholine challenge test is one diagnostic tool for asthma in which nebulized methacholine is inhaled and the extent of pulmonary bronchoconstriction is quantified by spirometry.

Introduction

Asthma is a chronic lung disease that affects 26 million Americans and involves symptoms of cough, dyspnea, wheezing, and chest tightness (CDC 2012). It is characterized by airway inflammation, reversible airway obstruction, and airway hyperresponsiveness (AHR) to triggers such as pollen. In addition to asthma, AHR is found in other diseases, including chronic airway obstruction, congestive heart failure, cystic fibrosis, bronchitis, and allergic rhinitis (Crapo et al. 2000). The methacholine inhalation test is one method to measure the degree of AHR.

Methacholine

Methacholine is a synthetic choline ester that acts as a nonselective muscarinic receptor agonist in the parasympathetic nervous system (Birnbaum and Barreiro 2007). Its binding to muscarinic M3 receptors on smooth muscle in the airways activates myosin and subsequent smooth muscle contraction (Davis and Cockcroft 2012). It is considered a direct stimulator (Cockcroft 2010).

Indications

Methacholine challenge testing is of the most diagnostic value in patients who present with a clinical history consistent with asthma but who have normal lung function on spirometry (Trepper et al. 2012). Because its negative predictive power is greater than its positive predictive power, a negative methacholine challenge can rule out a diagnosis of asthma (Crapo et al. 2000). Other uses for methacholine reactivity measures include monitoring responses in clinical trials with new therapies for asthma.

Contraindications

Because exposure to methacholine can result in bronchoconstriction, the methacholine inhalation test is contraindicated in patients with severe airflow obstruction. The American Thoracic Society (ATS) guidelines state an absolute contraindication of severe airflow obstruction, defined as FEV1 < 50 % predicted or < 1.0 l. A relative contraindication is moderate airflow obstruction, defined as FEV1 < 60 % or < 1.5 l.

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Additional contraindications include myocardial infarction or stroke in the last 3 months, uncontrolled hypertension, systolic blood pressure > 200, diastolic blood pressure > 100, or known aortic aneurysm. The relative contraindications include inability to perform acceptable-quality spirometry, current use of cholinesterase inhibitor medication, or pregnancy and nursing. Methacholine is a pregnancy category C drug (Crapo et al. 2000); that is, animal reproduction studies have shown adverse effect on the fetus, and there are no adequate, well-controlled studies in humans (FDA 2012).

Testing Methods

There are two common methods used to perform the methacholine test. While there is a difference in the method of dose delivery between the two, all other aspects are the same.

The first procedure is the 2-min tidal breathing method. Inhalation of aerosolized methacholine is performed through a jet nebulizer during a tidal breath of 2 min. The second method is the dosimeter nebulizer system. Deep inhalation of a breath triggers delivery of a certain concentration of aerosolized methacholine for a total of five breaths.

In brief, both methods initially begin with saline diluent as a baseline control. Then methacholine at a certain concentration is delivered with each breath. The concentration of methacholine is doubled from 0.03 mg/mL to 16 mg/mL as tolerated. There is a 5-min interval between the start of one inhalation and the start of the next inhalation. FEV1 measurements are made at 30 s and then 90 s after the completion of each inhalation. The difference between FEV1 using post-diluent and post-methacholine values is calculated with each breath. The test is stopped either when the FEV1 falls by 20 % or more from the postdiluent value (PC20) or after the highest concentration of methacholine is administered (Cockcroft 2009, Davis and Cockcroft 2012).

Recent studies have shown that there are discordant findings between these two commonly used methods. The deep inhalation of the dosimeter method has been found to result in more false positives than the tidal breathing method. The current recommendation is a submaximal inspiration instead of a deep inhalation if employing the dosimeter method (Cockcroft 2009, Davis and Cockcroft 2012).

Interpretation

After the methacholine test is stopped, the PC20 is interpolated from a log dose concentration curve. According to the ATS guidelines, the PC20 level categorizes AHR as follows: PC20 at a methacholine concentration >16 mg/ml is normal, 4–16 mg/ml is borderline, 1–4 mg/ml is mild, 0.25–1 mg/ml is moderate, and <0.25 mg/ml is marked AHR.

The interpretation of the methacholine challenge test is dependent on various factors. These include the presence of current respiratory symptoms, the degree of baseline airway obstruction, the quality of spirometry, and the pretest probability of asthma (Crapo et al. 2000). Some studies suggest the inclusion of patients with a baseline FEV_1 > 60 %, which according to the ATS guidelines is a relative contraindication (Davis and Cockcroft 2012).

False negatives can occur if testing of atopic patients occurs outside of the allergy season and if medications known to inhibit the test have been continued (Davis and Cockcroft 2012). Such medications include oral and inhaled bronchodilators, antihistamines, leukotriene modifiers, and foods, such as tea, coffee, cola drinks, and chocolate.

A PC20 that occurs at a methacholine concentration >16 mg/ml in a patient with a pretest probability of 30–70 % effectively rules out asthma. On the other hand, a PC20 that occurs at a methacholine concentration <1 mg/ml with the same pretest probability strongly suggests asthma. The highest combination of positive and negative predictive power occurs when the pretest probability is about 50 % (Crapo et al. 2000).

The pretest probability of asthma is the probability a person has asthma before

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the methacholine test is performed (AHRQ, Available from http://effective-healthcare.ahrq.gov/index.cfm/glossary-of-terms/?pageaction=showterm&termid=114). There is no formally accepted method of calculation. In practice, it is derived from a physician's clinical judgment, which includes history, physical exam, and laboratory data for an individual patient (Gilbert and Auchincloss 1990).

Conclusion

The methacholine challenge test is a useful diagnostic tool in patients with clinical symptoms suspicious for asthma but who have a normal spirometry. Currently, two relatively comparable methods, the jet nebulizer and dosimeter, are employed. In a patient with a pretest probability of 30–70 %, a PC20 at >16 mg/ml of methacholine effectively rules out asthma, while a PC20 < 1 mg/ml of methacholine strongly suggests asthma.

Cross-References

- ▶ Asthma Variants: Allergic Asthma
- ▶ Asthma Variants: Cough-Variant Asthma
- ▶ Methacholine Challenge

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Methods (In Vivo): Skin Test (Intradermal, Puncture)

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Synonyms

Allergy skin test; Immediate hypersensitivity skin test

Definition

Allergy skin tests are a method to evaluate the presence of IgE-mediated hypersensitivity to proteins termed allergens (pollens, food, drugs, etc.) which involves the introduction of the potential allergen into the skin and demonstration of a positive reaction (wheal and flare).

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Introduction

Skin tests are used to confirm sensitivity to specific protein substances called allergens. Features of skin tests are that they are technically simple, can be performed rapidly, are inexpensive, and have a high degree of analytical sensitivity (Demoly et al. 2009). Under certain conditions, false positives and negatives can occur.

Skin testing can be safely performed in all age groups by trained allergists. They serve as a useful diagnostic tool for establishing allergens that may be involved in chronic allergic rhinitis or hay fever, severe asthma, or suspected allergy to a food, drugs, or stinging insects. It can be used for evaluating clinical reactions and distinguishing IgE-mediated reactions from other types of reactions. The results of skin tests provide information about whether patient's symptoms are due to an immediate hypersensitivity to an allergen and provide guidance on treatment and avoidance. Results of skin testing are often used to determine the design of specific allergen immunotherapy or shots. Among the contraindications for performing skin testing are severe skin disease such as atopic dermatitis, inability to discontinue antihistamines, and the presence of uncontrolled asthma. A history of food-triggered symptoms and venom anaphylaxis are not contraindications for skin testing. However, recent anaphylaxis (within the last 4 weeks) to insect stings can result in false negatives.

Allergy skin testing was first introduced in 1865 by Blackley and has since remained a primary tool for the evaluation of IgE-mediated allergic disease (Blackley 1880; Demoly et al. 2009). Mantoux first used intradermal testing in (1908; Demoly et al. 2009). Lewis and Grant described the prick test in 1924, and the procedure was modified by Pepys in 1970s (Lewis and Grant 1924; Pepsys 1975; Demoly et al. 2009). Skin prick, puncture, and intradermal testing have been continued to be used and validated over the years (Demoly et al. 2009). Further, skin testing reagents have also been improved, and several are now standardized based on international standards for allergen extracts known as bioequivalent allergy units (Larenas-Linnemann et al. 2012; Slater et al. 2012; Turkeltaub et al. 1982).

Pathophysiology

Once allergen is introduced into the skin, it is bound by IgE residing on the surface of skin mast cells. In order to express allergen-specific IgE, an individual must have been previously exposed and generated an IgE antibody response, a process termed sensitization. The production of a wheal and flare response occurs through pro-inflammatory and neurogenic mediators which result in capillary dilation. Inflammatory mediators are released through allergen-induced skin mast cell degranulation. Allergen cross-linking of IgE-bound on the surface of skin mast cells results in mast cell degranulation of variety of mediators (Hamilton 2010). Histamine and tryptase are released from the skin mast cells within 5 min and peaks by 30 min (Shalit et al. 1990). Other agents such as substance P, neurokinin A, and calcitonin gene-related peptide (CGRP) have also been shown to produce dose-dependent wheals and flares (Demoly et al. 2009). It is known that antihistamines can significantly impair the skin test reaction, and therefore, antihistamines must be stopped by the patient several days or weeks prior to undergoing skin testing. In addition to being the major mediator in the wheal and flare response, histamine may also trigger release of substance P which may further stimulate skin mast cell degranulation through a positive feedback loop (Demoly et al. 2009).

Late or delayed skin responses involving erythema and inflammation are thought to be partially T cell mediated and can occur hours to days later at the site of testing. The classic late phase reaction is related to IgE, not IgG to a given allergen (Frew and Kay 1991; Demoly et al. 2009). The exact mechanism has not been characterized. Histamine, kallikrein, thromboxane B2, PGD2, LTC4, and platelet-activating factor have been recovered in skin biopsies of individuals with late phase reactions (Demoly et al. 2009). CD4+ T cells and other lymphocytes

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play a key role in the propagation of the late phase reaction through release of cytokines (Frew and Kay 1988; Demoly et al. 2009). Eosinophil activation and degranulation and release of RANTES and IL-4 also occur during the late phase reaction (Demoly et al. 2009). Late reactions generally peak at 6–12 h after allergen application and resolve within 24–48 h (Hamilton 2010).

Methods for Skin Testing

Epicutaneous (prick and puncture) and intradermal are the major methods used for immediate hypersensitivity skin testing.

Epicutaneous (Also Known as Percutaneous) Skin Tests

Skin testing is commonly performed on the forearm or back. During epicutaneous testing, a single drop of each allergen is usually suspended in glycerinated saline, and each control is placed on the surface of the skin (Hamilton 2010). A test device, which may be a hypodermic needle, solid bore bifurcated needle, or lancet that may have single or multiple points, is used to introduce the allergen (Erekosima and Saini 2012). Using the modified prick method, the needle or lancet is inserted at a 90° angle and gently lifted to 45° angle with care not to cause bleeding (Demoly et al. 2009). The skin is then gently lifted, creating a break in the epidermis which allows allergen to penetrate (Erekosima and Saini 2012). Excess allergen is then removed with gauze or tissue paper (Hamilton 2010). In contrast, the puncture method involves inserting the device through the drop at a 90° angle to the skin, but not to a depth so as to induce bleeding.

Prick-to-prick testing involves pricking an object, usually a fruit, then pricking the skin. This technique is sometimes used in the diagnosis of food allergy if a particular extract is not available or if the allergist has concerns for enzymatic degradation of extracts or absence of the relevant protein for testing (Dreborg 1988; Demoly et al. 2009).

A separate device is generally used for each allergen; however, the same needle may be used after cleansing with ethanol and saline (Kupczyk et al. 2001; Piette et al. 2002; Demoly et al. 2009). Allergen should be spaced at a sufficient distance, at least 2 cm apart, to avoid overlap of erythema (Demoly et al. 2003; Demoly et al. 2009). A positive control of histamine dihydrochloride (10 mg/mL) and a negative control of either saline or 50 % glycerinated human serum albumin are applied at the same time in order to asses for the validity of the test (Hamilton 2010; Erekosima and Saini 2012). The diameter of the wheal and erythema are measured in millimeters after 15–20 min, when they are generally considered to be at their maximum size (Demoly et al. 2009). The longest and orthogonal diameters are measured and then averaged. A positive result on prick/puncture testing is considered to be an average wheal of 3 mm greater than that seen with the negative control. Wheals smaller than 3 mm may reflect trauma or epidermal bleeding and thus are not considered positive. A scoring scale system (0 to 4+) is no longer used due to variability among different systems (Erekosima and Saini 2012). Several factors have been observed to result in variability in test results. These include the patient's biological responsiveness, the skill of the skin test performer, the equipment used, the extracts and their purity, and the methods for measurement of the wheal or flare diameter (Demoly et al. 2009; Hamilton 2010).

Intracutaneous (Also Known as Intradermal) Skin Tests

Intradermal testing is indicated when epicutaneous testing is negative in patients who otherwise have a history strongly suggestive of specific allergen sensitization. It may also be utilized in cases where particular allergen extracts are of low potency and it is especially utilized in assessing sensitization to venom and drug allergens. It is not used in testing the evaluation of food allergy due to concerns for adverse reactions. Unlike percutaneous testing which can be performed on either the back or forearm, intradermal testing is applied only to the forearm. This allows for the application of

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a tourniquet if systemic symptoms should occur (Lieberman 2006; Demoly et al. 2009; Erekosima and Saini 2012). The intradermal skin test requires approximately 1,000-fold lower concentrations of antigen than the epicutaneous skin test to produce a same-sized skin reaction (Hamilton 2010). Depending on the potency of the extract being used, the concentration may vary from 1/1000 to 1/100 (Demoly et al. 2009; Erekosima and Saini 2012).

Intradermal skin testing involves injecting allergen into the epidermis using a tuberculin syringe with a 26- to 30-gauge needle (Hamilton 2010). The skin is stretched and the needle is inserted at a 45° with the bevel up. The solution (0.01–0.05 mL) is injected once the bevel is completely under the skin (Erekosima and Saini 2012). Generally, a bleb measuring 2- to 3-mm diameter is produced when 0.02 mL is injected properly (Hamilton 2010). If a bleb does not appear, the injection was either too deep, too superficial, or not in sufficient quantity (Erekosima and Saini 2012).

In some cases, a skin test titration is performed which involves the administration of the same volume (e.g., 0.02 mL) of extract in a series of 3- or 10-fold dilutions into different sites in the skin (Hamilton 2010). This method identifies the concentration of an extract that produces a defined wheal or erythema diameter (e.g., 8-mm wheal) (Hamilton 2010). The greater the patient's sensitivity to the allergen extract, the lower the concentration of allergen that is required to induce the predefined wheal or erythema diameter (Hamilton 2010). In drug testing, duplicates of a single dose are placed at different sites as a further way of assessing for false positives or negatives. If results are discordant for the same drug, they are repeated in duplicate. The results are read at 15 min after application. A reaction larger than the negative control may indicate sensitization (Erekosima and Saini 2012). Grading has not been standardized, but a survey of board certified allergists revealed that 85 % use 3 mm above the negative control as the criterion for a positive intradermal skin test (Erekosima and Saini 2012).

Interpretation

Positive Results

A positive skin test reflects the presence of IgE antibodies and sensitization to the allergen tested, but does not necessarily prove clinical disease (Demoly et al. 2009). A careful clinical history with regard to onset of symptoms and triggers should be obtained and used to determine whether the skin test results reflect a true allergy. In fact, there is some evidence that positive skin tests occur at almost twice the frequency than subjects expressing clinical disease. In the United States, the prevalence of positive skin tests to one or more inhaled or airborne allergens is 54.3 % (Arbes et al. 2007), yet allergic rhinitis affects only 18 % of the population (Nathan et al. 1997). Dermographism, a condition which can result in whealing with firm stroking of the skin, can lead to a false-positive wheal and erythema reaction and confound the skin test result (Hamilton 2010). The presence of a positive saline response (>3 mm) during percutaneous testing may occur in individuals who exhibit dermographism and thus make the interpretation of positive results difficult.

Negative Results

The lack of a positive histamine response may indicate inadequate technique or histamine blockade through the prior administration of drugs such as newer-generation antihistamines (cetirizine, loratadine, fexofenadine, desloratadine, levocetirizine) and older-generation antihistamines (diphenhydramine, phenothiazine) or tricyclic antidepressants (Demoly et al. 2009). Drugs that affect the vasculature such as vasopressors can also potentially lead to negative results. Moreover, prolonged use of systemic steroids may lead to false-negative skin test results, whereas intranasal or inhaled corticosteroids do not alter skin testing results. Intranasal antihistamines should be held three days before testing. False-negative results may also occur in individuals with thin skin such as the elderly (King and Lockey 2003; Demoly et al. 2009) or those who are dehydrated.

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Side Effects and Risks

Itch may persist for 2–3 h and can be ameliorated by the application of topical hydrocortisone cream, an ice pack, or the ingestion of oral antihistamine following testing. It is not uncommon for patients to have a vasovagal response to a skin test which is typically manifested by light-headedness or skin pallor. Asthma exacerbations and systemic allergic reactions (anaphylaxis) have been reported, but are generally rare. In a study of children, the rate of generalized systemic reactions with fresh foods was 0.52 % and 0.26 % in adults (Demoly et al. 2009; Dreborg 1988; Codreanu et al. 2006). Therefore, due to the risks, the performance of skin testing requires a trained staff who is knowledgeable in the recognition and management of side effects such as anaphylaxis (Demoly et al. 2009).

Cross-References

- Allergen Immunotherapy, Overview
- Asthma Variants: Allergic Asthma
- Cutaneous Drug Reactions
- Diagnostic Components: Allergen for In Vivo (Skin Testing, Immunotherapy) and In Vitro (Serology) IgE Antibody Testing
- Food Allergens
- Oral Allergy Syndrome
- Venom Content
- Vespid Allergy: Yellow Jackets, Hornets and Wasps

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Methyldibromo Glutaronitrile, Contact Allergy to

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Synonyms

Contact dermatitis; Methyldibromo glutaronitrile

Methyldibromo glutaronitrile is a potent contact allergen, which is used as a preservative in a wide variety of products because of its antimicrobial properties. It can be found in all kinds of cosmetic and personal care products such as body, face, and hand lotions, sunscreens, baby lotions, shower gels, shampoos, massage oils, and even in toilet paper. Furthermore, it is also a common component of paints, cutting and drilling oils, polishes, cleaning agents, coolants, and glues. Because of its widespread appearance and increased sensitizing potential, it has been banned in leave-on products in Europe. Skin contact elicits a cutaneous delayed-type hypersensitivity reaction with erythema, swelling, vesicles, crusting, and desquamation in sensitized people.

Cross-References

► Allergic Contact Dermatitis

Methylisothiazolinone Allergy

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Synonyms

2-Methyl-4-isothiazolin-3-one; 5-Chloro-2-methyl-4-isothiazolin-3-one; Cl + Me-isothiazolinone; Euxyl k100; Kathon CG; Methylchloroisothiazolinone/methylisothiazolinone (MCI/MI)

Definition

The methylchloroisothiazolinone (MCI) and methylisothiazolinone (MI) are isothiazolinones used as a preservative. The most widely used commercial product is Kathon CG. It contains a mixture of MCI and MI in a 3:1 ratio and is approved for use as a cosmetic and toiletry preservative. MCI and MI can cause contact allergy. Although MCI is the more potent allergen in this combination, MI alone is an important emerging preservative allergen.

Introduction

Isothiazolinones are heterocyclic compounds used as biocides because of their antimicrobial properties against gram-positive and gram-negative bacteria, fungi, and algae. The methylchloroisothiazolinone (MCI; 5-chloro-2-methyl-4-isothiazolin-3-one; CAS 26172-55-4) and methylisothiazolinone (MI; 2-methyl-4-isothiazolin-3-one; CAS2682-20-4) in a 3:1 ratio by weight (MCI/MI) are the active ingredients in a preservative that is frequently used in topical products such as cosmetics and toiletries

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(Higgins et al. 2013). Its trade name includes Kathon CG. But there are several formulations marketed under various other trade names (e.g., Kathon 886, Kathon WT, Kathon 893, and Euxyl K100). These others, along with Kathon CG, are used as biocides in a variety of industrial products and systems such as latex emulsions, metalworking fluids, and water-cooling towers (Mowad 2000). Animal and clinical studies have shown that MCI and MI can cause contact allergy. However, MCI is the more potent allergen of both. Sensitization to MI is mainly thought to be acquired as an immunological cross-reaction after sensitization to MCI. However, isolated sensitization to MI also occurs.

Prevalence of Sensitization

Rates of contact allergy to MCI/MI rose to levels of up to 8 % when it was first introduced as a preservative in 1980 (Fewings and Menné 1999). This was thought to be secondary to high concentrations found in "leave-on" cosmetic products. This prompted more strict use concentration recommendations from expert panels. In the European Union, the concentration allowed is 15 ppm for rinse-off and leave-on products, whereas in the United States, a concentration of 7.5 ppm is permitted in leave-on and 15 ppm in rinse-off products. In some countries such as Japan, its use in rinse-off products is permitted, but not in leave-on products (Cuesta et al. 2010). It is also used in industry, where the concentrations can be higher.

Despite these modifications in use concentrations, sensitization prevalence to MCI/MI has remained fairly stable at 1–4 %, according to the European Surveillance System on Contact Allergy Network (Uter et al. 2012). In the United States, the North America Contact Dermatitis Group data indicate a stable frequency of positive reactions to MCI/MI from between 2.2 % and 3.6 % over the period from 2001 to 2010 (Warshaw et al. 2013). This allergen was the fifth most commonly positive preservative behind formaldehyde 1 % aq, quaternium 15.2 % pet., iodopropynylbutyl carbamate 0.5 % pet., and methyldibromoglutaronitrile/phenoxyethanol 2.0 % pet (Castanedo-Tardana and Zug 2013).

In the early 2000s, MI alone was introduced to industrial products; shortly after, the first cases of occupational MI contact allergy were published (Lundov et al. 2011). Many of the specific cases of MI contact allergy published were occupational cases or airborne contact allergy from paints or glues. In 2010, two studies were published with the first cases of cosmetic-related MI contact allergy (García-Gavín et al. 2010; Lundov et al. 2010). These studies reported MI contact allergy caused by rinse-off and leave-on products as well as wet wipes. Actually the use of MI as preservative alone is rising, and MI is an important emerging preservative. Because of the special concomitant exposure to MCI and MI in the past, sensitization to MCI and a cross-reactivity to MI are possible. However, there is now increased exposure to the weaker allergen MI at much higher concentrations than before, and often without concomitant exposure to MCI, resulting in an increased proportion of patients with primary sensitization to MI (Geier et al. 2012).

MI was permitted in cosmetic products with a maximum concentration of 100 ppm. There are no restrictions on the use of MI in industrial products, and the concentrations used are higher than those permitted in cosmetic products. Because MI is not routinely tested in the United States, there is no US data reporting the frequency of positive reactions to this allergen. However, the overall prevalence of contact allergy to MI in Europe has been shown to be in the area of 1.4–1.54 % (Castanedo-Tardana and Zug 2013).

Clinical Features

Exposure to MI and MCI can derive from both cosmetic and occupational sources. MI can be together with MCI or separate. The sensitization to these products is more common in females and in patients with facial, hand, or perianal dermatitis. Allergy to MCI/MI may present as acute dermatitis of rapid onset or as an exacerbation

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of preexisting dermatitis (Fewings and Menné 1999). The morphology is usually eczematous. On the face may be patchy and mimic seborrheic dermatitis. MCI/MI has also been reported in eyelid dermatitis. Most cosmetics responsible for allergic contact dermatitis to MCI/MI are leave-on products, and widespread dermatitis may be seen with the use of moisturizing creams and lotions. However, most products preserved with MI are in the rinse-off category. Wet wipes are a well-identified sensitization source for MI. It has been described to cause perianal allergic contact dermatitis in adults and napkin dermatitis and also hand dermatitis in patients when used either for their own personal hygiene or their babies.

Airborne allergic contact dermatitis and systemic contact dermatitis have been attributed to release from recently painted walls and from a toilet cleaner (Sasseville 2004).

In the occupational setting, MCI/MI can produce hand dermatitis after exposure to cutting oils preserved with it or in hairdressers from shampoos. Occupational exposure to MCI/MI can cause a caustic burn (Rietschel and Fowler 2008) on direct exposure to the undiluted product. This chemical burn led to active sensitization, followed by dermatitis on the affected parts. The most frequently affected are workers making paints or glues, laboratory technicians, printers, carpet makers, paper makers, house painters, and metalworkers. Painters constitute the majority of occupational allergic contact dermatitis cases to MI alone.

Patch Testing and Instructions for Patients

The determination of the most suitable concentration at which MCI/MI should be tested has been controversial. In most baseline series, MCI/MI has been included for years at a concentration of 100 ppm aq., which has been considered to be the optimum concentration required to the preservative with the fewest number of false-negative and irritant reactions. However, some studies established that patch testing to 200 ppm may diagnose more cases. This upper concentration has not showed an increase in irritant reactions or cases of active sensitization (Cuesta et al. 2010; Higgins et al. 2013).

Besides MCI and MI, there are also other isothiazolinones available for industrial products. Cross-reactions between MCI and MI with other isothiazolinones may occur, but they appear to be rare (Isaksson et al. 2008). The cross-reactivity in patients allergic to MCI/MI and MI has been investigated. MCI is the stronger allergen of the two, so a higher percentage of patients primarily sensitized to MI can be expected to have cross-reaction with MCI than vice versa (Geier et al. 2012). About half of the MI-allergic patients did not react to MCI/MI, providing further evidence that MI is an independent primary sensitizer (Lundov et al. 2013).

MI is not included in the European or US allergen screening series. The concentration of MI in the MCI/MI patch test substance (75 ppm MCI/25 ppm MI) is very low, and an MI allergy reaction could be missed by testing only MCI/MI (Castanedo-Tardana and Zug 2013). MI should be considered as a potential suspect allergen among patients with suspected cosmetic dermatitis, facial dermatitis, and sunscreen allergy. More studies are needed to establish the optimal patch test concentration, but the preliminary results suggest that 2,000 ppm is an appropriate patch test concentration (Bruze et al. 2013).

Patients with allergy to MCI/MI or MI should check carefully the labels in order to detect and avoid both chemicals, because of the possibility of cross-reactivity between them (Macias et al. 2013). However, avoidance of MCI/MI or MI can be difficult for patients because it is contained in many household products, or sometimes the cosmetics products do not have the full ingredient labeling. These preservatives are in common use in many shampoos, cleansers, and especially in cosmetic and skin care products.

Conclusions

MCI/MI is a preservative very common in cosmetic products and one of the most common causes of preservative contact allergy. MI alone is an important emerging preservative allergen.

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Its frequency of use in cosmetic products is on the rise. Both allergens should be considered particularly in patients with facial, hand, or perianal allergic contact dermatitis.

Because a concomitant positive reaction to MI and MCI/MI was seen in only about half of the patients, a positive reaction to MI could be missed by testing with MCI/MI and not with MI alone.

Cross-References

- ▶ Allergen Avoidance: Avoidance Strategies for Skin Allergies
- ▶ Allergic Contact Dermatitis
- ▶ Emergent Allergies in Cosmetics
- ▶ Preservatives Contact Allergy

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Microscopic Polyangiitis

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Synonyms

Microscopic PAN; MPA

Definition

Microscopic polyangiitis is a systemic vasculitis affecting the small- and medium-sized vessels which is associated with anti-neutrophil

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antibodies and classically presents with pulmonary and renal manifestations.

Originally, MPA was thought to be in the spectrum of polyarteritis nodosum (PAN) (Guillevin and Lhote 1995) which classically affects medium-sized vessels, but this entity, with features such as a glomerulonephritis and pulmonary involvement, was individualized over time to represent its own disease process (Feehally et al. 1987; Guillevin et al. 1993; Guillevin and Lhote 1995). MPA is often described as one of the "pulmonary-renal" syndromes indicating that inflammation is abundant in both the lungs and kidneys along with other symptomology. Other examples of pulmonary-renal syndromes include Goodpasture's syndrome, formerly called Goodpasture's disease, and granulomatosis with angiitis (formerly called Wegener's granulomatosis).

The vasculitides are a heterogenous group of disorders causing an inflammatory cascade with end organ damage. Blood vessels are the primary targets of these disorders and the type of vascular structure involved can help classify the disease process and lead to the particular diagnosis. Often a vasculitis can present with subtle or conflicting symptoms making diagnosis difficult. Occasionally a vasculitis can present with only a fever of unknown origin at its onset.

Pathogenesis

Vasculitis is thought to require an initial event that primes inflammatory cells and endothelial cells to fuel an inflammatory cascade. Proposed events include infection, allergic reactions, and antigen exposures although the true etiology is not known at this time. Although the different classes of vasculitis can affect vessels of different sizes and thus produce varied clinical syndromes, all are thought to end in inflammatory infiltrate, cell necrosis, and occlusion of vascular structures. One of the proposed mechanisms of vasculitis involves the formation of antibody-antigen immune complexes which then perpetuate inflammation and may cause cell injury and lysis.

As described above, MPA is associated with the development of ANCAs. The precise role of these antibodies in the development of vessel occlusion is not known. Some pro-inflammatory event may cause myeloperoxidase (MPO) and anti-proteinase III (PR3) to be expressed on cell surfaces of neutrophils and possibly endothelial cells (Guilpain et al. 2007). The binding of antibody to antigen may trigger an "activation" of the neutrophil, starting an inflammatory cascade. It has also been proposed that ANCAs may cause direct cytotoxic damage to endothelial cells expressing these proteins. Classically MPA is more associated with MPO antibodies or P-ANCA in a perinuclear distribution.

Diagnosis

Diagnosis is usually made with a combination of clinical indicators, antibody testing, and frequently with a tissue biopsy showing a small to medium vessel vasculitis. The tissue biopsied may include skin, pulmonary tissue, nerve, gastrointestinal tract, and most frequently glomeruli. Acute renal failure or palpable purpura can bring patients to acute medical attention often leading to biopsy.

Clinical Features

Clinical features of MPA present as a result of inflammation of small- to medium-sized blood vessels. The most common clinical manifestations include pulmonary, skin, and renal involvement. Pulmonary involvement can be seen in 25–55 % of patients. Manifestations include pulmonary hemorrhage, pleuritis, and interstitial lung disease (Chung and Seo 2010; Savage et al. 1985). Patients may complain of hemoptysis, chest pain, cough, or trouble breathing. Imaging can show ground glass opacities or interstitial lung disease (Collins and Quismorio 2005; Gomez-Puerta et al. 2009a, b). Interstitial lung disease can be seen as a result of long-standing inflammation.

Skin lesions are found in 30–60 % of patients and can be the presenting symptom (Chung and Seo 2010; Savage et al. 1985). Palpable purpura

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can be found in the dependent areas, particularly the lower legs (Kluger et al. 2008). In contrast to petechiae, purpura are raised non-blanching lesions often seen in the lower extremities and buttocks. Livedo reticularis can also be seen (Kluger et al. 2008) which is a lacy patterning of the skin often seen in patients with some type of vasculopathy. Biopsies of these areas often show leukocytoclastic vasculitis which is a nonspecific indicator of small vessel disease thought to be precipitated by immune complex deposition.

Renal involvement is common and seen in 80–100 % of patients (Chung and Seo 2010; Savage et al. 1985). The disease can range from asymptomatic to rapidly progressive disease requiring emergent dialysis. Clinically, patients present with edema, abnormal urine sediment, and microscopic hematuria. Red cell casts due to active glomerulonephritis can also be seen. Biopsy specimens of the kidney show a focal segmental necrotizing glomerulonephritis. Crescents, indicating massive glomerular necrosis, can also be seen in aggressive cases. In contrast to lupus, the biopsies do not show immunoglobulin deposition within the kidney and thus are deemed pauci-immune (Chung and Seo 2010; Savage et al. 1985).

Differential diagnosis for a case resembling vasculitis can be broad, but one should consider other conditions which cause damage to vasculature or mimic palpable purpura. These conditions include infections such as endocarditis and rickettsia, toxic substances like cocaine, and paraneoplastic phenomenon. Anti-phospholipid antibody syndrome can also be a mimicker as it can cause renal disease resembling glomerulonephritis, skin changes, and pulmonary hemorrhage.

Treatment

Treatment involves suppressing the immune system in order to control the inflammatory cascade. Most patients are initially treated with high-dose steroids which are toxic to inflammatory cells. Longer-term therapy in the past has involved medications which suppress the body's ability to make rapidly dividing cells such as azathioprine, methotrexate, or cyclophosphamide. These drugs can cause profound immunosuppression and can place the patient at risk for infections. Secondary cancers, such as leukemia, have also been reported with cyclophosphamide (Seo et al. 2005) perhaps from long-standing damage to the cellular components in the bone marrow. More recently the chimeric monoclonal antibody rituximab, an antibody to CD-20 which is a marker on maturing B cells, has been used with some success (Cartin-Ceba et al. 2012; Stone et al. 2010). Rituximab is thought to be less immunosuppressive and more targeted at the specific inflammatory cascade involved in disease. Relapses are common (Lhote et al. 1996; Guillevin et al. 1999) in the course of MPA, and patients need to be followed closely by a rheumatologist and other subspecialists.

Summary

Microscopic polyangiitis (MPA) is an idiopathic systemic vasculitis which commonly affects small caliber blood vessels such as capillaries, venules, and arterioles and is associated with the presence of anti-neutrophil cytoplasmic antibodies (ANCA).

Patients often develop vasculitis in the skin, lungs and kidneys although other organ systems can also be involved. Biopsy can be a helpful tool for diagnosis, and most patients require aggressive immunosuppression as therapy.

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Morphology and Histologic Identification of Mast Cells

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Synonyms

Diagnostic staining of mast cells in issues; Mast cell staining

Definition

Employment of various methods including cytochemical, immunochemical, electron microscopic, and flow cytometric techniques to visualize mast cells.

Introduction

Mast cells are cells of hematopoietic origin residing in tissues. They were first described in 1877 by Paul Ehrlich by their ability to stain metachromatically with basic aniline dyes (Ehrlich 1877). These dyes were later found to be detecting the acidic glycosaminoglycans such as heparin in mast cell granules.

It is very difficult, if not impossible to discern individually scattered mast cells by routine hematoxylin/eosin staining. By Wright-Giemsa staining routinely used for diagnostic hematology, tissue mast cells appear as round cells with a unilobular nucleus and dense basophilic granules occupying all of their cytoplasm. While the granular staining properties of mast cells may resemble basophils by routine staining, a number of important distinctions can be made. First, mast cells are not found in peripheral circulation under normal circumstances. Second, basophil nucleus is polymorphonuclear. Third, basophils have increased nucleus:cytoplasm ratio as compared to mast cells, and they possess fewer granules (Fig. 1).

Mast cells in tissues can be detected by a number of cytochemical, immunohistochemical, flow cytometric, and electron microscopic techniques.

Cytochemical Stains

Toluidine blue stain is a commonly used metachromatic stain used to identify mast cells in culture and in tissue sections, where the granules appear lighter purple in contrast to the darker blue nucleus. This stain can be used in a number of biopsy sections but is not reliable in bone marrow biopsies, as mast cells often lose their

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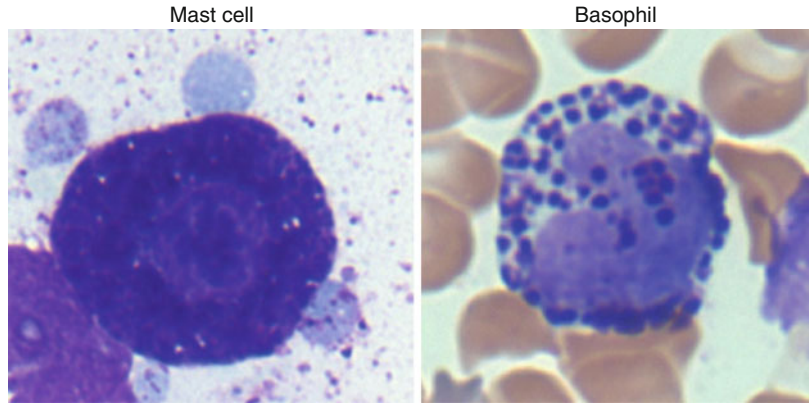

Morphology and Histologic Identification of Mast Cells, Fig. 1 Morphology of mast cell in a bone marrow aspirate and a basophil in peripheral blood as stained by Wright-Giemsa

metachromatic staining properties during routine processing including decalcification in an acidified medium. Likewise, aminocaproate acetate is a fairly specific stain for mast cells but requires special tissue processing (Li 2001). Chloroacetate esterase is a reliable stain to demonstrate mast cells in tissues where contamination from promyelocytes is not anticipated. Cytochemical stains rely on intact granular structure and their intensity may diminish if the mast cells are disrupted or degranulated either due to processing or pathologic conditions.

Immunohistochemical Identification

Recommended stains for histopathological identification of mast cells in human tissues are tryptase and CD117.

Tryptase

At least two distinct mast cell types are identified based on their location and protease content: connective tissue or constitutive mast cells (MCCT), whose numbers appear to be stable within a given tissue in a given individual, and mucosal mast cells (MCMs) which are recruited to the sites of inflammation such as intestinal mucosa upon triggers such as parasitic infections (Hallgren and Gurish 2011). Major proteases in MCCT include tryptase, carboxypeptidase, and chymase, while MCMs appear to have a more restricted protease phenotype primarily consisting of tryptase. Consequently, development of an antibody to detect tryptase was crucial in morphologic identification of mast cells in various tissues (Fig. 2). Tryptase expression in other cells is limited to basophils and myelobasts which express this protease in minute quantities (often <100 fold less than mast cells). Some mast cells with very immature phenotype (such as those found in mast cell leukemia and sarcoma) and theoretically immediately after a degranulation event may have less intense staining for tryptase. Commercially available antibodies for tryptase (such as AA1 and G3) allow immunohistochemistry to be performed in archived paraffin-embedded histopathologic tissues and are generally not affected by the decalcification process in bone marrow biopsies. While proteases in mice differ from those in humans in terms of nomenclature, mouse mast cell proteases 6, 7, and 11 are regarded as the equivalents of human tryptase.

CD117 (Kit)

CD117 marks the receptor for stem cell factor, the major growth and differentiation factor for mast cells. CD117 is encoded by the proto-oncogene c-kit. All mast cells express CD117 at high levels on their surface. In hematopoietic tissues, CD117 is also expressed by hematopoietic progenitors, albeit at a lower level. Other major cell types expressing CD117 include

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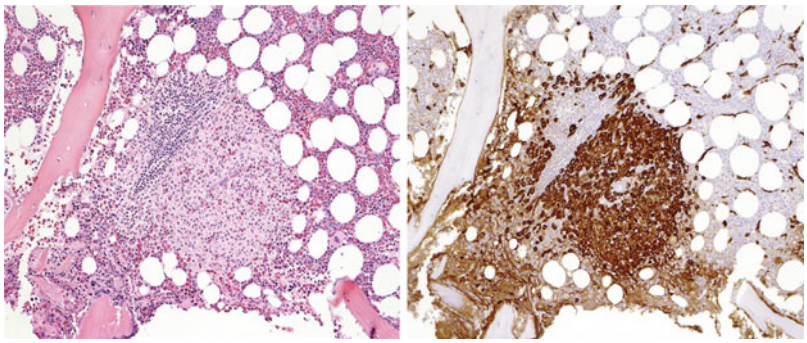

Morphology and Histologic Identification of Mast Cells, Fig. 2 Dense collection of mast cells as demonstrated by (**a**) H&E stain and (**b**) tryptase immunohistochemistry in a patient with systemic mastocytosis

melanocytes, gastrointestinal stromal cells, and germ cells. Therefore, while CD117 expression is highest on mast cells, it is not specific for mast cells. In pathologic tissues, CD117 is expressed by AML, ▶ mastocytosis, and gastrointestinal stromal tumors. CD117 staining can also be performed in archival tissue.

Flow Cytometry

Flow cytometry is a sensitive method of detecting in vitro cultured or tissue mast cells in single cell suspensions. Mast cells express high levels of CD117 and the high affinity IgE receptor on their surface. Therefore, mast cells can be detected as double-positive cells expressing both of these markers at high levels. In mast cell obtained from tissues, staining for surface-bound IgE can replace the staining for IgE receptor. It should be noted that basophils also express high levels of IgE receptor but should not be significantly positive for CD117. Likewise, hematopoietic progenitors (including CD34+ population) express intermediate levels of CD117 which are lower than mast cell expression of this marker. Normal mast cells also express a variety of other surface markers including CD45, CD33, CD43, CD44, CD54 but are negative for CD2, CD3, CD4, CD8, CD11b, CD14, CD15, CD16, CD19, CD20, CD21, CD25, CD31, CD35, CD56, or CD57 (Agis et al. 1996).

A number of concerns exist when identifying mast cells in bone marrow aspirates for diagnostic purposes (Akin et al. 2006). Mast cells are rare events and a considerably higher number of cells (ideally >500,000) should be counted as compared to routine diagnostic flow cytometry. However, availability of immunohistochemical stains for pathologic and normal mast cell identification in tissue sections (such as tryptase and CD25) may overcome the difficulty and expertise required for flow cytometry.

Electron Microscopy

Mast cells can be reliably distinguished from basophils and other cells by ultrastructural analysis by showing a specific pattern of crystal structure in mast cell granules, with heterogeneous with lattice and scroll-like patterns (Dvorak et al. 1983) (Fig. 3).

Mast Cell Morphology in Mastocytosis

Mastocytosis is a neoplastic proliferative disorder of mast cells (Fig. 2). Morphology and surface staining characteristics of mast cells display important differences in mastocytosis as compared to normal mast cells (Sperr et al. 2001). These differences are employed as diagnostic tools. Mast cells in mastocytosis often show aberrant cytoplasmic, nuclear, and granular properties. They may have an elongated (spindle shaped) cytoplasm with projections, eccentric and sometimes clefted or multilobular nucleus and lighter staining and sparser granules. Tryptase and CD117 stains identify the

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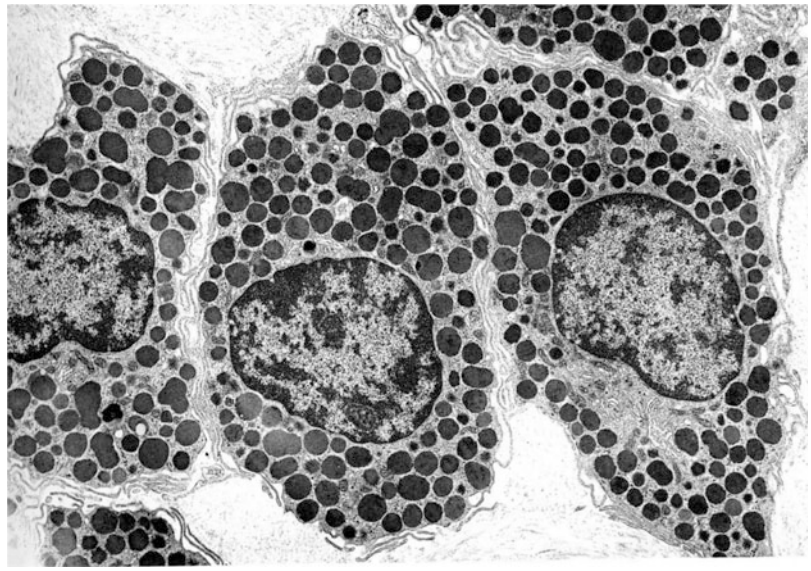

Morphology and Histologic Identification of Mast Cells, Fig. 3 Electron microscopy of skin mast cells (Courtesy of Dr. Mariana Castells)

mastocytosis mast cells with similar sensitivity to normal tissue mast cells. In contrast to normal tissue mast cells, mastocytosis cells aberrantly express CD25 (Escribano et al. 1998) which can be used as a reliable marker of clonal mast cell disease both flow cytometrically or immunohistochemically (Valent et al. 2001).

Cross-References

► Mastocytosis

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N

Nail Contact Dermatitis, Including Allergic Contact Dermatitis Due to Nail Cosmetics

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Synonyms

Contact dermatitis; Nail

Definition

Chronic paronychia and onycholysis can be signs of allergic contact dermatitis due to artificial nails or nail cosmetics, especially nail polishes. Typical allergens are acrylates in artificial nails and toluene sulfonamide formaldehyde resin, which comprises up to 25 % of nail polish. However, most of the allergic contact reactions against nail polishes manifest themselves not around the nails but at other body locations, which are often touched with the nails (mostly the face and the neck) or are affected by an airborne contact dermatitis due to the volatile nature of the allergens (often seen as eczema of the eyelids).

Cross-References

► Allergic Contact Dermatitis

Netherton's Syndrome

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Definition

Netherton's syndrome is a severe, genetic skin disease with similarities to atopic dermatitis. The syndrome is characterized by chronic skin inflammation, severe dehydration, and growth retardation together with universal pruritus. Netherton's syndrome shows an autosomal recessive pattern of inheritance. Recently, the genetic basis has been delineated. The cause of the disease is a mutation in the *SPINK5* gene. This gene encodes a serine protease inhibitor LEKTI. LEKTI is dysfunctional in these patients and results in a reduced inhibition of many serine proteases expressed in the skin. These proteases are involved in many aspects of skin homeostasis

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including lipid hydrolysis, desquamation, and remodeling. The disease severity is, therefore, determined by the level of LEKTI expression and is ranging from a complete absence of serine protease activities to milder forms.

The lesions are very susceptible to infection and the development of allergies. Therefore, the mortality rate is high. Treatment options are limited. Symptomatic treatment of the lesions represents the cornerstone.

Cross-References

► Atopic Dermatitis

Nickel Allergic Contact Dermatitis

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Definition

Nickel allergy is one of the most common causes of contact allergic dermatitis. The disease develops in locations where nickel-containing metal is touching the skin. Therefore, it is very common to observe the eczema at earlobes (from earrings), at the wrist (watch strap), and at the lower abdomen (jeans stud). The clinical reaction includes erythema, vesicles, scaling, and pruritus. In addition to the local reaction, systemic responses are also known. They result from dietary nickel ingestion. It has been reported that some nickel-allergic patients develop cutaneous reactions when they consume a high nickel diet, and, conversely, a reduction of dietary nickel intake may result in disease improvement.

These findings are the basis for the developing of a low nickel diet, where the following foods need to be avoided: canned fruits, dried fruits, nuts, beans, broccoli, peas and chocolate.

The diagnosis depends on patch testing with nickel sulfate hexahydrate. The therapy consists of topical anti-inflammatory treatment and nickel avoidance. The list of nickel-containing metals is growing every day. It consists of jewelry, personal articles like mobile phones, razors, lighters, handbag catches, clothing, metal items in the home and kitchen, silver coins, and metal at work.

Cross-References

► Allergic Contact Dermatitis
► 3-dimethylaminopropylamine (DMAPA), Allergic Contact Dermatitis to
► Eyes and Eyelid, Contact Allergic Reaction On
► Methods (In Vivo): Skin Test (Intradermal, Puncture)
► Nickel Allergic Contact Dermatitis
► Occupational Contact Dermatitis Due to Acrylates and Methacrylates
► Photoallergic Contact Dermatitis

Nickel Contact Dermatitis

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Synonyms

Allergic contact dermatitis (ACD); Contact hypersensitivity (CHS); Irritant contact dermatitis (ICD); Nickel allergy; Occupational contact dermatitis (OCD)

Definition

Nickel contact dermatitis is a common inflammatory skin condition characterized by erythematous and pruritic skin lesions after contact with

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this metal. It can be irritant or allergic. Irritant contact dermatitis (ICD) is caused by nonimmune-modulated irritation of the skin. In contrast, allergic contact dermatitis (ACD) is a delayed hypersensitivity reaction after skin exposure to nickel.

Introduction

Metals are the most common contact sensitizers, both in adult as pediatric population (Brandão and Gontijo 2012), especially nickel (Ni), a silver-colored metal used in a wide variety of industrial and consumer products, including stainless steel, magnets, rechargeable batteries, coinage, keys and tools. It is also widely used in metal alloys, such as nickel steels and nickel cast irons, nickel brasses and bronzes, and alloys with copper, chromium, aluminum, lead, cobalt, silver, and gold. Because of its resistance to corrosion, nickel is also used for plating, and it has been occasionally used historically as a substitute for decorative silver.

It began to affect the general population in the mid-twentieth century when nickel was incorporated into products such as clothing fasteners, suspenders, and costume jewelry. The first case of allergic contact dermatitis (ACD) caused by nickel was described in a plating industry worker in 1889 (Blascho 1889), it was initially considered an occupational contact dermatitis (OCD); however, nickel use quickly spread to the manufacture of multiple products, facilitating the beginning of nickel dermatitis cases among consumers, mainly related to the use of wristwatches and spectacle frames (McAlester and McAlester 1935). At present nickel is the most common allergen-causing contact sensitization. Fashion and lifestyle play an important role in the development of this sensitization. In the last decades, costume jewelry, especially earrings introduced at an early age and more recently new contact sources as piercing and mobile phones, has contributed to increasing the sensitization to nickel.

Patients allergic to metals are often allergic to more than one metal. It has been suggested a co-sensitization mechanism due to contamination of various metals in consumer objects (Ruff and Belsito 2006).

Primary nickel sensitization is related to a continued and direct skin contact with nickel-releasing consumer products, although it may also occur on the hands, following occupational exposure.

Nickel contact dermatitis represents an important morbidity that can produce a decrease in the quality of life and lead to inability to work. Consequently its management is of great importance.

Epidemiology

Nickel sulfate is the number one allergen in frequency of positive patch test reactions and an important cause of allergic contact dermatitis (ACD) in the general population, affecting 17 % of women and 3 % of men in Europe and North America (Thyssen et al. 2007). Most cases of ACD are due to non-occupational exposure. As an occupational disease, it particularly affects men, but the number of women with occupational exposure is increasing. This gender difference is traditionally explained by increased exposure in women, as the result of direct skin contact with nickel-releasing metal such as in costume jewelry and clothing accessories. A genetic predisposition possibly plays a role as well as the loss-of-function mutations in the filaggrin gene are likely to increase the risk of nickel allergy (Thyssen et al. 2008).

Although nickel allergy has been an increasing problem over the past decades, recently, studies with general population in Denmark have suggested a decrease of nickel allergy among Danish women, which is likely to be an effect of the regulation on nickel exposure (Thyssen et al. 2009).

Nickel Use and Exposure

Nickel ACD occurs when metallic items, corroded by human sweat, release free nickel ions that act as haptens, inducing sensitization. Sensitization to

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nickel can occur from skin contact with jewelry and consumer products, from occupational exposure and by means of experimentation. It can occur either by exogenous (skin contact) or endogenous exposure (oral or inhalation). The most important factor for the induction and elicitation of cutaneous nickel allergy is the amount of nickel per unit area present in the epidermis that it be quantified as $\mu g/cm^2$ (Lidén et al. 2011). In the 1990s, the European Union legislated a limit of 0.5 $\mu g/cm^2$/week of nickel release from nickel-containing alloys and coatings. According to this directive, a decline in the prevalence of nickel allergy was observed in some countries. However, despite these new regulations, nickel is still the most common allergen detected by patch testing all over Europe.

Furthermore, it has been suggested that the amount of nickel released from an alloy in synthetic sweat is a more significant risk factor for nickel allergy than the total concentration of nickel in the alloy. Metallic items such as buttons and earrings known to induce and elicit allergic nickel dermatitis released large amounts of nickel in synthetic sweat. Currently only a minor part of nickel is used in items designed to be in prolonged skin contact.

Ear piercing is the most common cause of sensitization and therefore represents an important risk factor for nickel allergy (Fischer et al. 1984). Other common sources of sensitization are costume jewelry, jeans buttons, zippers, belt buckles, fasteners, wristwatches, metal accessories, coins, magnets, keys, and door handles.

Stainless steel and white gold usually release less than 0.5 $\mu g/cm^2$/week, but can trigger or aggravate ACD in previously sensitized individuals.

Nickel can be found in washing liquids and powders, and other household products, but these only exceptionally cause dermatitis, particularly hand eczema in nickel-sensitized individuals.

Nickel also could be present as a contaminant in cosmetics, though rarely may cause facial dermatitis in sensitized individuals.

Orthodontic appliances can occasionally induce nickel ACD (cheilitis, perioral eczema, and stomatitis). However, nickel sensitization is lower in adolescents who wear dental braces before ear piercing, suggesting an induction of immune tolerance by mucosal exposure to nickel (Van Hoogstraten et al. 1991).

It is unclear if metal plates utilized in orthopedic surgery could sensitize or exacerbate a preexisting nickel allergy and even lead to rejection of joint replacements. However, it has been agreed that nickel allergy is not a contraindication for the application of a stainless steel replacement.

Food is an important source of nickel; significant nickel concentration was found in mixed nuts, dried fruits, tea bags, cocoa, chocolate, soy products, legumes, wholegrain flour, and shellfish.

Extremely sensitive nickel patients may develop a systemic reaction from ingestion of nickel in tap water or foods cooked in nickel-containing cooking utensils (Nielsen et al. 1990).

Clinical Manifestations

Allergic reactions may occur suddenly or after months of being exposed to nickel. The classic clinical presentation of dermatitis caused by nickel is a primary eruption, characterized by recurrent eczematous lesions on the sites of direct contact with the items that release nickel, such as earlobes (earrings), wrists (watches), neck (necklaces), and umbilical region (jeans button). Other areas such as the face and scalp can be affected from contact with cellular phones, piercing, and hair clasps. A 30–40 % percent of people sensitive to nickel develop hand eczema, which appears to be aggravated when there is concomitant allergic to cobalt. In most cases, it is difficult to differentiate the lesions clinically and histopathologically from atopic or irritant dermatitis.

In sensitized individuals, transcutaneous, inhalatory, intravenous, or oral exposure to nickel can cause a **systemic allergic contact dermatitis** (Jensen et al. 2006). It has a latency period of a few hours to a few days after exposure and is often underdiagnosed. Clinical features include maculopapular exanthema, vesicular hand eczema, flexural dermatitis, and flare-up

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reactions at earlier sites of contact dermatitis. Rarely does it cause noneczematous dermatitis, such as urticarial reactions and vasculitis-like lesions. The maculopapular exanthema with flexural involvement presents as a symmetrical eruption in neck, face, eyelids, elbow flexures and forearms, hands, inner thighs, and anogenital regions. and it may be generalized. The "baboon syndrome" is an infrequent form of systemic contact dermatitis, characterized by a classical distribution pattern of maculopapular erythematous lesions, located in the gluteal and flexural regions (Andersen et al. 1984).

Occupational Allergy

Nickel is potentially an important occupational allergen, especially in the plating industry where its exposure is significant. Occupations commonly linked with nickel-associated dermatitis include metal work (production of stainless steel, nickel alloys, and nickel cast iron), electroplating and electroforming, decorating, and enameling in the ceramics industry, batteries, and coin manufacture. Other occupations such as hairdressers, nurses, jewelers, dental technicians, cleaning staff, and cashiers are potentially at risk, but the relevance of occupational nickel exposure on contact dermatitis in these occupations is often questioned (Torres et al. 2009).

Primary sensitization usually occurs from non-occupational sources and work exposure aggravates the dermatitis, but occasionally primary sensitization occurs in the workplace.

Nickel occupational contact dermatitis (OCD) appears most commonly as hand eczema, as a result of the continued exposure of the hands to work tools that release nickel. Generally 30–40 % of patients with occupational nickel allergy develop chronic hand eczema. To manage it, apart from the preventive and therapeutic strategies, it is required to improve the workplace environment eliminating and substituting metallic tools. It is also necessary to increase labor hygiene and promote the use of personal protective equipment (polyvinyl chloride gloves).

Nickel allergy can cause inability to work. Sometimes it might be necessary to temporarily remove the worker from his tasks or even to rehabilitate the worker in another function without nickel exposure.

Diagnosis

History and Clinical Examination

A complete and detailed clinical history is essential in the diagnosis of dermatitis, including possible source of exposure and a complete employment history. Clinical findings that increase diagnostic suspicion include recent onset, aggravation of previous dermatitis, and location of the lesions in typical sites that usually coincide with areas exposed to metal objects.

Furthermore, systemic allergic contact dermatitis should be suspected in chronic cases of nickel dermatitis with vesicular hand eczema where external nickel exposure is excluded.

Patch Testing

The most useful and reliable method for the diagnosis of nickel ACD is the patch test, which is safe and reproducible. The standard patch test includes nickel sulfate at concentrations of 2.5 % (North America) and 5 % (Europe) in petrolatum. The TRUE Test® also uses nickel sulfate and tends to elicit stronger reactions. Nickel is the most common positive patch test allergen, and it has been estimated positive in 10–30 % of female patients. Although sensitivity and sensibility of patch testing is not exactly known, reproducibility is usually elevated. There is a strong correlation between patch test results and clinical history of nickel exposure. Nevertheless a positive test reaction is not necessarily an indicator of clinical disease. False-positive reactions may occur in atopic patients, where follicular irritative reactions are common. False-negative reactions can also appear. In case of strong clinical suspicion, the test can be repeated using penetration enhancers such as dimethyl sulfoxide (DMSO).

Patch testing is considered to be safe in children using the same concentration as in adults, although some authors recommend a lower allergen concentration (Wahlberg and Goossens 2001).

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Active patch test sensitization from nickel sulfate 5 % in petrolatum has never been documented.

Quantification of Nickel Exposure

It is consequently important, in the case of a positive patch test reaction to nickel, to trace the source of primary sensitization, evaluate previous and current exposure to metal items in direct skin contact, and measure personal and occupational exposure using the dimethylglyoxime (DMG) spot test, the acid wipe sampling methods, the finger immersion test, and other exposure measurements.

Other methods less useful in the diagnosis of nickel sensitivity include the lymphocyte proliferation test, prick (indicated in cases of contact urticaria due to nickel) and intradermal test.

Preventive Strategies

Avoidance of Nickel

The only way to prevent recurrence is avoiding skin contact with metallic items that release nickel. This strategy achieves a decrease in the frequency of hand eczema in nickel-sensitive individuals. Patients should be instructed to identify those objects that release nickel in order to avoid them. The DMG spot test is a simple method commercially available, which identifies metallic objects that contain high nickel concentrations by a color change in the solution applied on the item tested. An object that gives a negative result is unlikely to induce the dermatitis.

Therefore, patients should avoid costume jewelry and use gold or stainless steel objects. Those metallic items that cannot be avoided should be covered with enamel, adhesive tape, or nail varnish.

Cosmetic frequently include nickel, so that it is recommended "nickel-free" makeups that contain less than 1 ppm of nickel and can be safely used by most sensitized patients.

Prevention and Legislation

Regulating nickel release from consumer items designed to be in direct and prolonged skin contact efficaciously will prevent nickel dermatitis.

In 1990 Denmark established guidelines to regulate consumer nickel exposure and determined that metallic items should not release more than 0.5 mg nickel/cm^2/week. Subsequent results indicated a decreased frequency of nickel allergy among young subjects in the general population (Thyssen 2011). In 1994, the European Union established a regulation according to the Danish nickel guidelines. Finally, in recent years, the EU Nickel Directive dictated that coated products covered by the directive should not release more nickel than 0.5 μg nickel/cm^2/week within their first 2 years of use.

These major public health interventions were expected to change the epidemiology of nickel allergy and dermatitis in Europe.

Symptomatic Treatments

There is no specific treatment for nickel ACD, and the most effective method is to avoid the allergen. Untreated, lesions can persist several weeks despite the interruption of contact with the allergen.

The standard treatment includes oral antihistamines and topical corticosteroids. Oral steroids act as immunosuppressive agents and might be indicated for short-term treatment of severe dermatitis.

Topical immunomodulators such as pimecrolimus and tacrolimus provide a steroid-sparing option. Topical or oral antibiotics must be prescribed in case of a secondary bacterial infection. Emollients in creams are useful to relief itching and dry skin. Acute exudative or bullous lesions can be treated with antiseptics. Some patients with chronic ACD can benefit for PUVA. Alitretinoin, an oral retinoid, is a new option in the treatment of chronic and refractory hand dermatitis acting as anti-inflammatory and immunomodulator. Chelating agents and other substances can be used to bind nickel or reduce its penetration through the skin and thus to reduce the symptoms in subjects with nickel sensitivity. Disulfiram can chelate nickel but should be considered only in nickel-sensitized patients with severe hand eczema refractory to all other treatments as it can cause severe side.

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Barrier creams act as an "invisible glove," protecting the skin from environmental allergens and are effective in nickel allergy, particularly in patients with hand dermatitis.

In case of standard treatment failure, some patients may benefit from a nickel-free or a low-nickel diet (Antico and Soana 1999).

It is possible to induce immune tolerance to this metal using oral hyposensitizing treatment, although its efficacy has not been proven yet.

Prognosis

Nickel ACD is usually a life-long condition, but preventing contact with items that release this metal improves the prognosis. Factors associated with a bad prognosis include continuous nickel exposure, involvement of the hands, secondary bacterial infection, history of atopy, and multiple contact allergies (Kalimo et al. 1997).

Conclusion

Allergy to nickel is a global problem that affects a large number of patients. ACD due to this metal represents great morbidity and produces a decrease in the quality of life, so early diagnosis and proper management is fundamental. Finally, it is necessary to adopt preventive measures to reduce exposure in consumer objects and working environments.

Cross-References

- ▶ Allergic Contact Dermatitis
- ▶ Cobalt Contact Dermatitis
- ▶ Contact Dermatitis Due to New Metals
- ▶ Nickel Allergic Contact Dermatitis

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Nitroglycerin Dermatitis

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Synonyms

Contact dermatitis; Nitroglycerin

Glyceryl trinitrate (nitroglycerin) can be topically applied as a patch to induce systemic vasodilatation or an ointment around the anus to relax the muscle tonus of the sphincter ani and thus relief the pain due to anal fissures. While delayed-type hypersensitivity sensitization to nitroglycerin is not a common event, it can be the cause of chronic anal eczema, which often is misdiagnosed due to other potential trigger factors such as localized microbial infection or chronic irritation of the fissure. Patch testing will reveal the allergic reaction.

Cross-References

► Allergic Contact Dermatitis
► Contact Dermatitis Due to Topical Drugs

Nonasthmatic Eosinophilic Bronchitis

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Synonyms

Eosinophilic bronchitis; Nonasthmatic eosinophilic bronchitis (NAEB)

Definition

NAEB is a condition characterize by chronic cough, airway eosinophilia (>3 % in sputum), and absence of airway hyperresponsiveness.

Introduction

NAEB is an important cause of chronic cough and can coexist with other conditions such as eosinophilic lung diseases, allergic rhinitis, and chronic obstructive pulmonary disease. Despite airway eosinophilic infiltration resulting in sputum eosinophilia, patients have normal pulmonary function and bronchoprovocation challenge testing (Gibson et al. 1989). The etiology of NAEB and the reason for the lack of airway hyperresponsiveness in this condition are unknown.

Historical Background

Gibson et al. first described NAEB in 1989 in seven patients with corticosteroid-responsive chronic cough without abnormalities in airway function and sputum eosinophilia (Gibson et al. 1989).

Epidemiology/Prevalence

Large-scale epidemiologic data on NEB is not available, and the incidence and prevalence of NAEB in the United States remain to be determined.

In a 2-year cohort study of patients with an isolated chronic cough lasting more than 3 weeks (Brightling et al. 1999), ninety-one patients with chronic cough were identified among 856 referrals made to a single respiratory physician by primary care providers. NAEB was the primary diagnosis for cough in 12 (13.2 %) patients. After treatment with inhaled steroids, cough improved in all 12 patients. In eight patients, repeat sputum induction was performed 4 to 8 weeks after

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treatment was begun and showed a significant decrease in the sputum eosinophil count.

Pathogenesis

The primary cause of transmural airway eosinophilic inflammation in NAEB is poorly understood. However, extrinsic production of eosinophil chemotactic factors such as interleukin-5 resulting from a Th2 pattern of T-cell activation, airway chemotactic factors infiltration with increased release of vasoactive mediators, and basement membrane thickening has been described to be present in both asthma and NAEB, but infiltration of the airway smooth muscle by mast cells is noted only in asthmatics (Brightling et al. 2002a), which may explain the differences in airway hyperreactivity (Brightling et al. 2002b; Brightling 2006). Also, high prostaglandin E2 levels in the lower airways of patients with NAEB has been postulated to have protective effects against inhibition of bronchial smooth muscle cell proliferation and the development of bronchial hyperresponsiveness (Sastre and del Pozo 2012).

Clinical Manifestations

Patients commonly present with chronic intermittent dry cough of more than 2 months responsive to systemic or inhaled corticosteroid treatment. The prevalance of atopy in NAEB is the same as in the general population and heightened cough reflex sensitivity is common. Airway hyperresponsiveness and response to bronchodilators are absent (Brightling 2006). On follow-up, while patients may remain asymptomatic after therapy, some may develop asthma (Rytila et al. 2000).

Diagnosis

Once chronic cough is recognized in the absence of other causes including but not limited to laryngopharyngeal reflux, respiratory tract infections, upper airway cough syndrome, use of angiotensin-converting enzyme inhibitors in the setting of eosinophilia on sputum and/or bronchial wash fluid, normal chest film and spirometry findings, and no evidence of airway hyperresponsiveness, the diagnosis of NAEB is strongly considered especially after improvement in the cough following corticosteroid therapy.

Management

In NAEB treatment with inhaled corticosteroids, avoidance and abatement of potential environmental triggers remains the mainstay of therapy.

In patients with sustained chronic cough despite medical therapy, speech language pathology may be useful in mitigating cough reflex hypersensitivity often observed in NAEB patients (Ryan et al. 2010).

Cross-References

▶ Asthma Variants: Cough-Variant Asthma

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Nutrition in Food Allergy

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Synonyms

DRI, Dietary Reference Intake; FALCPA, Food Allergy Labeling and Consumer Protection Act of 2004; FDA, Food and Drug Administration; IgE, Immunoglobulin E; RD, Registered Dietitian

Definition

Management of food allergies in children involves education and careful monitoring of nutritional status. Education is essential for a patient and family to identify sources of the offending allergen(s), to understand how to read a food label, and to plan meals eaten at home and away from home. Monitoring of growth and careful examination of diet are important to ensure nutritional adequacy of a restricted diet.

Nutrition and Food Allergy

When an individual is diagnosed with a food allergy, the key to management is strict avoidance of the offending allergen(s). Education is important for compliance and for a nutritional balanced diet. A Registered Dietitian (RD) can provide education and support to achieve appropriate growth for infants, children, and teens and to provide nutritional adequacy to a restricted diet. Without education, the risk of accidental ingestion of the food allergen(s) increases. Education has been shown to improve quality of life for those individuals with food allergies.

When an infant, child, or teen has to follow a restricted diet, growth needs to be monitored closely. Removing entire food groups from a child's diet can reduce overall caloric intake. When a child has to avoid more than one food, it may be difficult for that individual to consume adequate calories. Close monitoring of the growth chart and analysis of food records are tools to monitor nutritional adequacy. Additional nutritional counseling may be necessary to achieve adequate growth.

Information about the food(s) to be avoided needs to include the different forms of that food, label reading, and potential sources of cross-contamination. Education may include alternatives or substitutes for the food to be avoided to ensure nutritional adequacy. Some individuals with food allergies may need nutritional supplements to meet nutrient needs. These supplements may be beverages or additives or supplements.

Nutritional Adequacy

For a child with food allergies, careful assessment of the diet helps to determine adequacy of that diet. If a child is allergic to one food, the nutritional adequacy of the diet may be uncompromised. For example, the child who must avoid shellfish may be able to consume adequate calories and protein. In this situation, this child may not require a multivitamin or any mineral supplementation. Without shellfish, the child may consume a well-balanced diet. If a child is allergic to multiple foods, the restrictions may impair the child's diet. For example, a child who avoids milk, egg, and peanuts has more foods to avoid. The overall caloric consumption may be affected. The intake of protein, calcium, and vitamin D may be less than the Dietary Reference Intake (DRI) for age. This child may need fortified alternatives and/or a multivitamin with minerals to meet the DRI for age.

In a study published in 2002, Christie found children with two or more food allergies were shorter than those children with a single food allergy (Christie et al. 2002). Suboptimal intake of calcium, vitamin D, and vitamin E was found in one quarter of the children with food allergies.

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Children allergic to milk and children with two or more allergies were at the greatest risk for inadequate nutrition (Christie et al. 2002).

Avoidance of Foods

Milk Allergy

If a milk allergy is suspected in a baby, avoidance of cow's milk is recommended. If the mother is exclusively breast-feeding, the mother should remove all cow's milk from her diet. A milk and dairy elimination diet for a lactating woman requires nutritional counseling to ensure that the mother receives adequate calories, protein, calcium, and vitamin D.

If a milk allergy is suspected in a baby who is formula fed, an extensively hydrolyzed protein formula like Alimentum or Puramino is recommended until 1 year of age. Soy-based formula is not recommended. In a study, about 14 % of children with an IgE-mediated milk allergy could not tolerate soy, and 30–50 % of the children with enterocolitis reacted to soy protein (Ziegler et al. 1999). Goat's milk is not recommended because of the potential cross-reactivity with the protein in cow's milk (Bellioni-Businco et al. 1999). Goat's milk and cow's milk both contain beta-lactoglobulin.

If the baby continues to have symptoms on a protein-hydrolyzed formula, an amino acid-based formula is recommended. Neocate from Nutricia, EleCare from Abbott Nutrition, or Puramino from Mead Johnson are currently available in the United States. Amino acid-based formulas are available in powder form only. These products are not readily available in drug stores or grocery stores.

Hydrolyzed protein formulas and amino acid formulas are nutritionally complete at appropriate volumes for age. Babies taking these formulas as their sole source of nutrition or as their primary source of calories once baby food is introduced do not generally need additional vitamins or minerals. With nutritional counseling, these formulas may be used beyond 12 months of age.

Nutritional counseling is essential to guide how a family chooses baby foods. Most single-ingredient baby foods are milk-free. Some dinners, biter, or teething biscuits may contain milk as an ingredient. If a milk allergy continues as the infant becomes a toddler, nutritional counseling is important to ensure adequate calories, protein, calcium, and vitamin D. If the toddler begins to refuse a hydrolyzed protein formula or an amino acid formula, an adequate diet can be devised with a milk substitute and protein from meats, beans and peas, grains, and vegetables. Milk substitutes are made from rice, soy, hemp, oat, and almond. Many have added calcium. A calcium and vitamin D supplement may be required to meet nutrient needs.

Egg Allergy

Avoiding egg because of a food allergy is more complicated than just eliminating scrambled, fried, and hard-boiled eggs from breakfast. As an ingredient, egg used can be found in a wide variety of foods such as bakery products, sauces and salad dressings, breaded meats, and pasta. Egg serves to emulsify foods like mayonnaise and sauces. Egg is used as a binding agent in meatloaf, meatballs, and croquettes. When beaten into foam, egg aerates desserts like meringue and mousse. Egg is a leavening agent in sponge cake and soufflés. An egg wash may add gloss to a bakery product when brushed on the top. Many chicken nuggets and strips are dipped in egg before they are coated with flour.

An egg-free diet may not contain adequate calories. Avoiding all foods with egg may decrease the overall caloric intake. Egg is a source of protein. When egg is removed from the diet, protein can be derived from meats, dairy, beans, and peas.

To enhance the variety of an egg-free diet, specialty foods or alternatives may be necessary. Egg-free mayonnaise is available in specialty grocery stores. Egg substitutes are not safe for those allergic to egg because they are made of egg white, vegetable oil, and yellow food coloring. These products were created for those following a low-cholesterol diet. Egg substitutes are readily available in grocery stores. However, egg replacers are safe products for individuals with egg allergy. These specialty products are

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available in powder form and can be used for baking. Egg replacers are found in specialty stores. The Food Allergy and Anaphylaxis Network provides these substitutes for egg in a recipe when baking:

- 1 tsp. baking powder, 1 T. liquid, and 1 T. vinegar. Add vinegar last.
- 1 tsp. yeast dissolved in 1/4 cup warm water.
- 1 1/2 T. water, 1 1/2 T. oil, and 1 tsp. baking powder.
- 1 packet gelatin and 2 T. warm water. Do not mix until ready to use.

Each combination equals 1 egg in a recipe. These substitutions may be used in recipes that require 1–3 eggs.

Soy Allergy

Soy is consumed in this country as tofu or soybeans such as edamame. Soy is used in "meat analogs," which are made from soy protein and grains. Some of these meat analogs contain egg and/or milk. Soy meat alternatives are made to resemble meats or poultry products in appearance. For example, a sausage link for vegetarian diet may have soy as its primary ingredient. Soy is also found as an ingredient in many commercially prepared foods. Processed meats, protein bars and powder for protein drink mixes, frozen entrees, and soups may contain soy as an ingredient. Many products to increase calories sold in health food stores contain soy as a protein source. Soybean oil and soy lecithin are generally well tolerated in individuals allergic to soy because the protein is removed in the processing (Bush et al. 1985).

A balanced diet is possible when avoiding soy. Many families limit processed foods to avoid soy. For example, many families choose to make homemade soup instead of canned or dried soup to avoid soy. Vegetarians who are allergic to soy can create a well-balanced diet using beans, peas, and lentils. These foods are grouped together and referred to as pulses.

Wheat Allergy

Wheat is a primary grain in the United States. Wheat is found in bakery products, cereals, noodles, and breaded meats. Wheat serves as a thickener in sauces and soups. Other grains may be substituted in the diet of an individual with wheat allergy. Products are available made from potato, rice, corn, and tapioca. Ancient grains like quinoa and amaranth are also available in specialty markets.

Many wheat products are fortified with iron and B vitamins. Many individuals with a wheat allergy use some of the same products made for people with celiac disease who avoid wheat, barley, and rye. Many gluten free foods are not enriched with iron and vitamins. A nutritional assessment could determine if the diet is low in iron and B vitamins. Other foods could provide these nutrients in the diet. For example, meat could be the primary source for iron. A multivitamin with iron could be used to meet nutrient needs.

Peanut Allergy

Peanuts are found in snack foods like crackers and trail mixes and desserts. Peanuts may be an ingredient with salads and soups. Peanut butter is an important food to many children and is served in daycares and schools. Peanuts are used in the cuisines of many Asian and African countries. Individuals with peanut allergy are advised to avoid tree nuts because of the risk of cross-contamination. Peanuts and tree nuts are often shelled and packaged on shared equipment. Particles of peanuts may be mixed with particles of tree nuts and created a food that is not safe for the individual with an allergy to either peanuts or tree nuts. Ice cream parlors may be a major source of cross-contamination for individual with peanut allergy. Peanut toppings can become mixed with candy toppings when an ice cream is made. Peanut oil that is highly processed is generally well tolerated in individuals with peanut allergy because the protein is removed during the processing (Taylor et al. 1981). Cold-pressed peanut oil contains peanut proteins and should be avoided.

Nutrients like vitamin E, B vitamins, magnesium, and manganese are found in peanuts. To provide an adequate diet, other foods like whole grains, fortified cereals, meats, and legumes could be emphasized in the diet of an individual with peanut allergy to provide nutrients available in peanuts.

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Tree Nut Allergy

Tree nuts include almonds, Brazil nuts, cashews, hazelnuts, macadamia nut, pecans, pine nuts, pistachio, and walnuts. Nutmeg and water chestnuts are not tree nuts and are generally safe for individuals with tree nut allergy. Sunflower and sesame are seeds and are not classified as tree nuts. Coconut is not considered a tree nut. Tree nuts are used in cereals, desserts, pastries, and crackers. Sauces like steak sauce may contain tree nuts. Gourmet nut oils often contain protein and could cause a reaction. The protein is not eliminated during processing of the nut oils. Walnut oil sold in a specialty store is an example.

Many allergists advise individuals allergic to tree nuts to avoid peanuts and other tree nuts because of the increased likelihood of cross-contamination during processing. Peanuts and different tree nuts are commercially shelled and packaged on shared equipment. Many individuals with one specific tree nut allergy have an increased chance of having an allergic reaction to another nut.

Some allergists evaluate individuals to each specific tree nut to determine which are safe to consume and which cause a reaction. For example, an individual may only be allergic to walnuts and can safely eat pecans grown from trees on their own yard.

Tree nuts contain protein, B vitamins, vitamin E, and magnesium. Meat and legumes could provide protein. Fortified cereals, whole grains, and vegetable oils could provide those vitamins and minerals for individuals with tree nut allergy.

Fish and Shellfish Allergy

Foods that may contain fish or shellfish include sauces and salad dressing. Caesar salad dressing and Worcestershire sauce contain fish. Soups or casseroles may contain fish. Asian restaurants may use fish sauce as flavoring ingredients in other meat dishes. Imitation crab often called surimi is made of fish and should be avoided.

Some individuals may tolerate one fish and be allergic to another. The risk of cross-contamination is great. Cross-contamination could occur at the coast when fish is unloaded from boats or in a restaurant when fish is cooked. Often there is shared equipment like grill tops and fryers. Generally, individuals with fish allergy should avoid all fish.

Shellfish can be divided into two distinct groups. Mollusks are clams, oysters, and scallops. Crustaceans are shrimp, crayfish, crabs, and lobsters. Again, the risk for cross-contamination is great because the cook in a restaurant may substitute one shellfish for another or a soup or casserole may contain a variety of shellfish. A grill top may not be adequately cleaned from cooking shrimp for one order to cooking chicken for the individual with a shellfish allergy. Imitation crab may be made from fish and contain crab flavoring which would make it unsafe for an individual with shellfish allergy.

Other Allergies

The eight major allergens account for 90 % of the allergies diagnosed in the United States. Individuals may be allergic to meats like beef, chicken, or pork. Others may have allergic reactions to seeds like sesame or sunflower. Sesame is an emerging allergy (Stutius et al. 2010). It is estimated that there are over 160 different food allergens. Education about strategies to avoid these foods is crucial. Individuals must contact manufacturers to determine if these other allergens are present. A nutritional assessment is important to determine if the restricted diet is nutritionally adequate.

Food Labeling in the United States and Europe

The United States Congress passed the Food Allergen Labeling Consumer Protection Act (FALCPA) of 2004 to ensure that individuals could identify food ingredients that may cause an allergic reaction on a label. This act also known as Public Law 108–282, Title II is a useful tool to those with many food allergies and their families.

Since January 01, 2006, all food products regulated by the Food and Drug Administration (FDA) must have a label that identifies the eight major food allergens: milk, egg, fish, crustacean shellfish, tree nuts, wheat, peanuts, and soybeans.

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These eight allergens were specified because these foods account for 90 % of food allergies in the United States. Under FALCPA, the allergen must be listed plainly so that the consumer can identify it easily. There are two ways that foods can be labeled:

- By placing the word "Contains" followed by the name of the food source from which the major food allergen is derived immediately after or next to the list of ingredients. For example, a manufacturer may place the words "Contains milk and wheat" below the ingredients.
- By placing the common or usual name of the allergen in the list of ingredients followed by a parenthesis by name of the food source from which the allergen is derived. For example, a manufacturer may place the word "eggs" in the body of the text.

FALCPA applies to all packaged food sold in the United States and regulated by the Food and Drug Administration (FDA). Foods manufactured in this country and foods manufactured outside of the United States and imported into this country must abide with this law. Meats, poultry, and some egg products are not included because these foods are regulated by the United States Department of Agriculture. Fresh produce is not included. In the case of tree nuts, fish, and shellfish, the specific type must be identified. For example, a label must identify if the food product contains walnuts or cashews or pecans.

Since the current labeling law requires companies to use either the "Contains. . ." phrase or the usual name in the text of the ingredients, individual with food allergies and/or their families should continue to carefully read both the list of ingredients and the declaration statement that begins "Contains. . .." Food manufacturers may choose to voluntarily add advisory warnings on food packages. These warnings indicate that foods may share equipment or that foods may be processed in the same facility. Foods with these advisory warnings, such as "this product may contain trace amounts of allergen," should be avoided (NIAID Guidelines 2010).

The legislation has been extremely useful to those with the eight major allergens. For those individual with allergies to sesame or mollusks, information on a food label may not be clear. Individuals with allergies other than the major eight or in addition to the major eight allergens must contact the manufacturer directly to confirm the presence of a specific allergen.

In Europe, legislation requires the eight major allergens be listed on the label just as the FALCPA. European guidelines have added the following foods to their label for cereal: gluten, mollusks, lupine, celery, mustard sesame, and sulfites (Taylor 2006). The sulfites must be listed if their amount present exceeds 10 mg/l/kg. Lupine is derived from a plant and often added to wheat flour for batters and breading.

Quality of Life

Avoidance of food allergens can affect quality of life in significant ways (Sicherer et al. 2001). A restricted diet impacts an individual by limiting meals eaten away from home, by limiting participation in social gathering, and by increasing anxiety associated with eating. Flokstra-de Blok and colleagues studied teens with food allergies. The teens reported decreased overall health and less energy (Flokstra-de Blok 2010). These teens described more restrictions on social events because of food allergies and restricted diets. Decreased quality of life may be a reason that some adolescents make choices to eat foods that are identified as allergens (Sampson 2006). In this study, 174 people were interviewed. Fifty-four percent of those interviewed reported eating a potentially unsafe food and did not describe the ingestion as accidental. Forty-two percent of those interviewed were willing to eat a food labeled "May contain. . ." and take the risk of consuming an allergen.

Education and counseling can help pediatric patients; especially adolescents develop strategies to cope with food allergies. Pediatric patients need to know how to describe what food they need to avoid in restaurants and social settings. Continued education for school personnel and food service staff can enhance knowledge for those responsible for meal preparation and snacks to create safe eating environments for young people.

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Summary

In Guideline 23 from the *Guidelines for the Diagnosis and Management of Food Allergy in the United States*: *Summary of the NIAID-Sponsored Expert Panel Report*, the Expert Panel recommends nutritional counseling and regular growth monitoring for all children with food allergies (Guidelines 2010). Education is essential to the avoidance of allergens for children with food allergies. A Registered Dietitian can provide information to children and their families to minimize accidental ingestion, to understand labeling laws and how to read labels, and to plan a nutritionally adequate diet. A Registered Dietitian can help children and their families to plan social events like birthday parties, school parties, and meals eaten away from home to minimize accidental ingestion.

Cross-References

- ▶ Cow's Milk Allergy
- ▶ Egg Allergy
- ▶ Food Allergy, Overview
- ▶ Peanut Allergy

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O

Occupational Contact Dermatitis Due to Acrylates and Methacrylates

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Synonyms

Occupational allergic contact eczema due to acrylates; Occupational allergic dermatitis due to acrylates

Introduction

Acrylates are chemicals (plastic materials) of low molecular weight, formed by the polymerization of monomers of acrylic or methacrylic acid (Campos et al. 2013).

They were introduced in industry in the 1930s and thereafter introduced into the medical field and also into the home environment (Pérez-Formoso et al. 2010).

In 1941 the first case of allergic contact dermatitis caused by methacrylates (Stevenson 1941) was published.

At certain concentrations, in addition to causing allergic contact dermatitis (ACD), these compounds can also produce irritative lesions of the skin and mucous membranes.

Since 1985, cases of allergic contact urticaria, rhinoconjunctivitis, and occupational asthma (Reig Rincón de Arellano et al. 2006) have been reported in the literature.

Methyl methacrylate is a lipid solvent powder, which can quickly penetrate into tissues and cause direct damage to the abundant nerve endings in the periungual area (Böhling et al. 1977).

Definition

Occupational ACD is an eczematous skin disorder caused by sensitivity to existing substances in the workplace (Alonzo and Rodríguez Peñaloza 1999).

Prevalence

The estimated prevalence of sensitization to acrylates in dentists and dental technicians varies between 5 % and 10 %; this is the most affected group, followed by industrial workers engaged in painting and coating, printing industry workers, workers in fiberglass, and professional beautician (s) (Constandt et al. 2005; Drummet 2002).

In 1994 in the USA, 3.1 billion dollars were spent on "artificial nails", which at that time were worn by about 19 million Americans. Their use increased over time at an annual rate of 6 %, and in 2002, sales of these items totaled $645 million in beauty salons (Kanerva et al. 2000).

ACD caused by acrylates is an increasingly common allergy in dermatology clinics, and it has labor and therapeutic implications.

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The last decade has seen an increase in ADC due to acrylates in relation to artificial nails made with preformed plastic parts which are placed with cyanoacrylate-type instant adhesive on the nail plate – "sculptured nails" or "porcelain nails" – formed by a mixture of liquid acrylic monomer with a polymer and cured at room temperature. In recent years, a new type of artificial nail has become popular, "gel nails," made of multiple layers of acrylic gel with each layer hardened by exposure to a source of ultraviolet light (Fisher et al. 1957). Consequently, this type of occupational ACD affects people handling these chemicals such as professional beautician(s) as well as their clients (Roche et al. 2008).

Ethiopathogenesis

The acrylic compounds used are acrylates, cyanoacrylates, and methacrylates.

Cyanoacrylates are also called "superglues"; these substances are widely used as contact adhesives for metals, glass, rubber, plastics, textiles, and biological materials (including fabrics to bind and bandages to close wounds in surgery, particularly orthopedic) (Pérez-Formoso et al. 2010).

Studies in the medical literature show affinities of class II molecules as a predisposing factor for the subsequent development of occupational disease (Jones et al. 2004), including studies suggesting that specific alleles such as DQB +0501 confer susceptibility to develop IgE to organic acid anhydride (Young et al. 1995), and also as a protective factor against low molecular weight allergens (Mapp et al. 2000; Horne et al. 2001). All of the above is explained by the fact that the context of the patient is what determines the expression of the genotype.

Clinical Picture

Allergic reactions to artificial nails may occur months to years after use, among both professional beauticians and users. Sensitivity to acrylates in professional beautician(s) generally affects women and consists of eczematous lesions of subacute or chronic type, located in the pads of their hands that have direct contact with the acrylic resin (Lazarov 2007).

Skin lesions affect the pads of the first three fingers of the nondominant hand, as these areas of the hand of the professional hold the hand of the client while the dominant hand holds the brush. Also very common are dorsolateral eczematous lesions on the hands of the professional because this area tends to rest on the work table and the furniture has remnants of acrylic resin (Campos et al. 2013).

Eczematous lesions may appear elsewhere on the body due to contact of monomer residues comprising the liquid adhesive or contact of polymer powder (which can contain monomer residues) with other areas of the skin or through airborne contact. Nail files may also contain small amounts of monomer that do not react completely until after 24 h (Tosti et al. 1991).

Symptoms present in professional beautician(s) are pruritus, paresthesia and pain when the ezcema evolves with cracks (Fisher and Baran 1991).

Clinical manifestations of users differ from those of professional beautician(s). At onset there is an itching sensation at the base of the nail, called Reiner symptom, and then paronychia, nail pain, and sometimes paresthesia. The base of the nail is dry and thickened and exhibits onycholysis (Ikeda et al. 1998).

It is important to know that "sculptured nails" should not be worn for more than 3 months and the period without using them must be of at least 1 month, since it is very common for the nail to be damage, with thinning and changes in coloring, as a result of improper maintenance and frequent filing with a powerful abrasive (Campos et al. 2013). Symptoms such as painful paresthesias are worrisome since this sometimes can be associated with burning or shooting pain that patients report as very unpleasant and may persist for years. Frequently, numbness and tingling are associated with paresthesias. Paresthesias appear most of the time in ACD, but sensitivity to acrylates appears not to be a requirement for its occurrence (Campos et al. 2013).

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Sometimes eczematous lesions resolve in a few months without treatment or preventive measures (Ikeda et al. 1998).

Diagnosis

To arrive at an early and effective diagnosis, it is crucial to complete a good medical history and conduct the proper tests at an early stage to locate the sensitizing agent causing the disease and to request any tests needed for early diagnosis.

It is indicated in patients who have symptoms compatible with eczema and in patients disclosing any working environment where acrylates are handled, such as beauty shops and industrial settings, particularly those related to printing (Pérez-Formoso et al. 2010).

The main test is patch testing adhered to back of the patient for 48 h. The results are read at 48 and 96 h following the criteria of the International Contact Dermatitis Research Group (Pérez-Formoso et al. 2010).

Additional to the baseline series of contactants (multiple contactants in order to make a differential diagnosis with other chemicals handled or detect co-sensitivities or cross-reactivities), it is possible to patch test:

- Commercial acrylate
- Specific acrylates that the patient handles at work, such as glues (Pérez-Formoso et al. 2010), or the scraping of the substance mixed with etanol or petrolatum jelly (Varela et al. 2001)

According to the literature, patch test positivity to acrylates can decrease in intensity as the weeks go by (Varela et al. 2001).

Cross-Reactivity Between Acrylates

It is clear from multiple published studies that there may be cross-reactivity between some acrylates:

- Hydroxyethyl methacrylate and ethylene glycol methacrylate (Pérez-Formoso et al. 2010)
- Ethylene glycol dimethacrylate and hydroxyethyl dimethacrylate A

In a series of 15 patients, the authors found sensitivity to multiple methacrylates but noted the absence of cross-reactivity between cyanoacrylate and the rest of these compounds (Roche et al. 2008).

It is important to bear in mind the possible cross-reactivity between these chemicals. The use of some acrylates is common in the home, and since they are highly sensitizing, they can cause subclinical sensitization in some subjects. Subsequently, if they handle acrylates in their work, occupational ACD may occur with the accompanying economic and labor impact involved for the patient as well as his or her employer (Pérez-Formoso et al. 2010).

Prevention

Workplace hygienic measures should be in place for workers who handle these substances on a daily basis and in every way possible to prevent the onset of allergic as well as irritating symptoms.

Good prevention requires the formation of multidisciplinary teams (occupational physicians, allergists, dermatologists, and prevention technicians) to work in unison in the development of comprehensive and effective prevention plans (Pérez-Formoso et al. 2010).

Physical protection at work, such as masks, gowns, and 4H gloves, is most important for primary and secondary prevention, since gloves made of latex, vinyl, nitrile, and polyethylene are not protective (Campos et al. 2013; Roche et al. 2008).

Using double nitrile or polyethylene gloves under nitrile gloves allows adequate protection for tasks that do not exceed 30–60 min (Campos et al. 2013).

Occupational ACD caused by acrylates is usually associated with chronic eczema on workers' fingers and causes disability for normal work of these patients since these chemicals pass through both rubber and plastic gloves (vinyl or nitrile). Therefore, in cases of occupational ACD caused by acrylates, the only prevention possible is the complete and utter removal of the patient-worker

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from the workplace, that is, from radical contact with acrylates. This should be accompanied by maximum hygiene measures to prevent sensitization to these compounds by other workers in successive exposures to avoid triggering the ACD symptoms caused by these compounds (Pérez-Formoso et al. 2010).

A number of published studies in the medical literature state that withdrawal of patients from the workplace is necessary to resolve ACD in those who work with acrylates.

An alternative option in patients using acrylates adhesives is to switch to an adhesive that does not contain them once the skin lesions of workers have healed. Since acrylates are irritants and patients have some skin atrophy, chafing can cause cracks that can lead to an increase in symptoms such as pain and precipitate complications such as infections (Pérez-Formoso et al. 2010).

In patients who are not yet sensitized, it is important to follow good personal protective measures, such as using alcohol-resistant gloves made of polyethylene, natural rubber. Gloves must also be replaced regularly, especially after close contact with acrylates. It is also important to apply a protective cream to the skin beneath the glove in order to act as a protective barrier, in case that the glove becomes torn due to its continued use. The worker must know that when handling acrylates, the use of protective eyewear is also required (Pérez-Formoso et al. 2010).

Treatment

As with any occupational disease, the best treatment is correct and exhaustive prevention.

Once there is an occurrence of occupational ACD due to acrylates, healing will occur with the total and absolute separation of worker from the usual work where acrylates are handled.

The treatment of complications will take place when they occur; although we do not have an effective treatment for paresthesias (Campos et al. 2013), there is treatment for skin infections associated with ACD.

Cross-References

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- ▶ Allergic Contact Dermatitis
- ▶ Fingernails from Sensitization to Acrylic, Loss of

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Ocular Antihistamines

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Synonyms

Ocular antihistamines; Ophthalmic antihistamines

Definition

Ocular antihistamines decrease the histamine-stimulated vascular permeability in the conjunctiva resulting in a decrease of ocular edema and suppressing the wheal response (Owen et al. 2004). Due to this mechanism, ocular antihistamines are approved to treat allergic conjunctivitis and ocular pruritus. Ocular antihistamines are often utilized to specifically treat ocular symptoms due to fewer limited adverse effects and rapid onset of action (Bielory et al. 2005; Spangler et al. 2003). In addition to antihistamine properties, the ocular antihistamines also present with mast cell stabilization and decongestant properties (Bielory et al. 2005); see Table 1 for a list of available ocular antihistamines.

Mechanism of Action

Histamine modulates hypersensitivity reactions, and, in particular, histamine causes the formation of ocular edema and the wheal response. Antihistamines are inverse agonists that bind to the histamine 1 (H_1) receptor and shift the conformation to the inactive state. H_1 antihistamines inhibit the histamine-stimulated vascular permeability in the conjunctiva and prevent the formation of ocular edema and wheal response (Owen et al. 2004).

Mast cell stabilizers result in the suppression of activation and infiltration of eosinophils, which decreases the degranulation of mast cells and prevents the release of histamine and other chemotactic factors. This prevents the subsequent exposure to allergens. Decongestants act on alpha-adrenergic receptors in the arterioles to produce vasoconstriction, which reduces redness and congestion.

Dosing

Multiple ocular antihistamines are available for the treatment of allergic conjunctivitis and ocular itching. Some agents are available generically and over-the-counter. See Table 1 for dosing, indications, and available strengths. There are no dosage adjustments for renal or hepatic dysfunction. Most agents have a pregnancy category C, except alcaftadine and emedastine which are pregnancy category B. It is unknown

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Ocular Antihistamines, Table 1 FDA-approved ocular antihistamines (Zatidor® prescribing information 2002; Patanol® prescribing information 2007; Bepreve® prescribing information 2009; Lastacaft® prescribing information 2010; Emadine® prescribing information 2011; Elestat® prescribing information 2011; Optivar® prescribing information 2010

Generic/ brand name(s)	Class	Indications: dosing (strength available)	Common adverse reactions	Special populations
Alcaftadine/ Lastacaft	Antihistamine/ mast cell stabilizer	Allergic conjunctivitis: 1 drop into each affected eye daily (3 mL, 0.25 %)	Headache, burning, pruritus, irritation, redness, stinging	Elderly: no dosage adjustment Children: safety and effectiveness have not been established in children < 2 years
Azelastine/ Optivar	Antihistamine/ mast cell stabilizer	Allergic conjunctivitis: 1 drop into each affected eye twice a day (6 mL, 0.05 %[a])	Headache, transient burning, stinging, pruritus, bitter taste, eye pain	Elderly: no dosage adjustment Children: safety and effectiveness have not been established in children < 3 years
Bepotastine/ Bepreve	Antihistamine/ mast cell stabilizer	Allergic conjunctivitis: 1 drop into each affected eye twice a day (5m L, 1.5 %; 10 mL, 1.5 %)	Headache, irritation, taste abnormalities, possible hypersensitivity reactions	Elderly: no dosage adjustment Children: safety and effectiveness have not been established in children < 2 years
Emedastine/ Emadine	Antihistamine	Allergic conjunctivitis: 1 drop into each affected eye up to 4 times in a day (5 mL, 0.05 %)	Headache, hyperemia, abnormal dreams dermatitis, keratitis, pruritus, unpleasant taste	Elderly: no dosage adjustment Children: safety and effectiveness have not been established in children < 3 years
Epinastine/ Elestat	Antihistamine/ mast cell stabilizer	Allergic conjunctivitis: 1 drop into each affected eye twice a day (5 mL, 0.05 %[a])	Headache, burning sensation, hyperemia, pruritus, folliculosis, rhinitis, sinusitis	Elderly: no dosage adjustment Children: safety and effectiveness have not been established in children < 2 years
Ketotifen/ Alaway, Zaditor	Antihistamine/ mast cell stabilizer	Allergic conjunctivitis, ocular itching: 1 drop into each affected eye twice a day at least 8–12 h apart (5 mL, 0.025 %; 10 mL, 0.025 %[a])	Rash, photophobia, mydriasis, keratitis, lacrimation disorder, itching, allergic reactions, burning, stinging, dry eyes, eye pain, discharge	Elderly: no dosage adjustment Children: safety and effectiveness have not been established in children < 3 years
Olopatadine/ Pataday, Patanol	Antihistamine/ mast cell stabilizer	Allergic conjunctivitis/ Patanol: 1 drop into each affected eye twice a day at least 6–8 h apart (2.5 mL, 0.02 %[a]) Pataday: 1 drop into each affected eye daily (5 mL, 0.1 %)	Headache, cold syndrome, pharyngitis, nausea, taste perversion, weakness, back pain, blurred vision, burning, conjunctivitis, dry eyes, eye pain	Elderly: no dosage adjustment Children: safety and effectiveness have not been established in children < 2 years

[a]Available generically

whether these agents are excreted into breast milk; therefore, caution must be used. Pediatric allergic conjunctivitis is common (La Rosa et al. 2013), and available medications are for use in ages 3 years and older.

Pharmacokinetics

Ocular antihistamines typically have an onset of action of within 3 min and duration ranging between 8 and 12 h. They have minimal systemic

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Ocular Antihistamines, Table 2 FDA-approved ocular antihistamines: pharmacokinetics (Zatidor® prescribing information 2002; Patanol® prescribing information 2007; Bepreve® prescribing information 2009; Lastacaft® prescribing information 2010; Emadine® prescribing information 2011; Elestat® prescribing information 2011; Optivar® prescribing information 2010)

Active ingredient	Onset of action	Duration of action	Absorption	Distribution	Metabolism	Excretion
Alcaftadine	–	–	Minimal	40 % protein bound (60 % for the active metabolite carboxylic acid)	Non-CYP 450 cytosolic enzymes ($t_{1/2}$ approximately 2 h)	–
Azelastine	Within 3 min	8 h	Minimal	–	–	–
Bepotastine	Within 3 min	Up to 16 h	Minimal	Approximately 55 % protein bound	Minimal, via CYP enzymes	Urine (approximately 75–90 % as unchanged drug)
Emedastine	Within 3 min		Minimal	–	$t_{1/2} = 3$–4 h	–
Epinastine	3–5 min	8 h	Low systemic absorption	Approximately 64 % protein bound	<10 % ($t_{1/2} = 12$ h)	Urine (55 %), feces (30 %)
Ketotifen	Minutes (unspecified)	8–12 h	Minimal	–	–	–
Olopatadine	–	–	Low systemic absorption	Approximately 55 % protein bound (primarily albumin)	Minimal ($t_{1/2}$ approximately 3 h)	Urine (60–70 %, mostly as unchanged drug), feces (17 %)

absorption; are typically protein bound, ranging from 40 % to 64 %; and have different half-lives depending on the agent. See Table 2 for pharmacokinetic information on the specific medications (Zaditor® prescribing information 2009; Patanol® prescribing information 2007; Bepreve® prescribing information 2009; Lastacaft® prescribing information 2010; Emadine® prescribing information 2011; Elestat® prescribing information 2011; Optivar® prescribing information 2010).

Drug Interactions

Drug interactions have not been studied with ocular antihistamines. Currently the only known medication of this group that is metabolized by the CYP P450 system is bepotastine. Because of topical administration and the overall dose is decreased, systemic administration is expected to be low. Drug-drug interactions will not likely be clinically relevant (Zatidor® prescribing information 2002; Patanol® prescribing information 2007; Bepreve® prescribing information 2009; Lastacaft® prescribing information 2010; Emadine® prescribing information 2011; Elestat® prescribing information 2011; Optivar® prescribing information 2010).

Adverse Reactions

The limited systemic absorption leads to limited systemic adverse effects. Adverse reactions associated with ocular antihistamines are localized (Owen et al. 2004) and include headache, burning, pruritus, irritation, redness, and stinging upon instillation. See Table 1 for adverse effects associated with each agent.

Clinical Application and Comparative Efficacy

Ocular antihistamines are approved for the treatment of allergic conjunctivitis and ocular itching. Multiple randomized controlled trials have shown that they are more efficacious than placebo (Owen et al. 2004; Bielory et al. 2005; Torkildsen and Shedden 2011; Greiner et al. 2011).

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Many formulations of ocular antihistamines include mast cell stabilizer properties (Table 1), and mast cell stabilizers have also shown improved efficacy over placebo (Owen et al. 2004).

A systematic review of nine double-blind, randomized controlled trials showed that ocular antihistamines provide benefit in treating seasonal allergic conjunctivitis compared to placebo (Owen et al. 2004). This review also evaluated eight double-blind, randomized controlled trials comparing ocular antihistamines with ocular mast cell stabilizers, and the authors did not find convincing evidence to support one medication versus another.

Olopatadine was found to be statistically more effective in reducing ocular itching than mometasone and fexofenadine at 3 and 5 min after a conjunctival allergen challenge. There was a trend towards improvement in conjunctival redness compared to fexofenadine and mometasone (Spangler et al. 2003).

Conclusion

Ocular antihistamines are an effective class of medications for the treatment of ocular manifestations of allergy-based diseases. They offer the advantage of direct application which results in decreased systemic absorption and decreased incidence of adverse effects normally seen with oral antihistamines. Due to their decreased systemic absorption, drug-drug interactions are unlikely. Some of the listed ocular antihistamines have decongestant and mast cell stabilizing properties, which contribute to their overall effectiveness.

Cross-References

- ▶ Intranasal Antihistamines
- ▶ Intraocular Vasoconstrictors
- ▶ Ocular Corticosteroids
- ▶ Oral Antihistamines
- ▶ Topical Antihistamines

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Ocular Corticosteroids

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Synonyms

Intraocular glucocorticoids; Ocular glucocorticoids; Ocular steroids; Ophthalmic corticosteroids

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Definition

Corticosteroids have been commonly used for the treatment of various allergic disorders. Ocular corticosteroids are an effective short-term treatment option for seasonal allergic conjunctivitis (SAC). Moreover, they have been reported to be the most effective in the treatment of severe and chronic forms of ocular allergy, providing effective relief of a broad range of symptoms of ocular inflammation (Bielory 2008). Corticosteroids exert their rapid anti-inflammatory effects within 6 h of application via interactions with glucocorticoid receptors (Stahl and Barney 2004). Targeted local delivery, high local concentrations, lower total steroid dose, and fewer systemic side effects are some of the advantages of local ocular corticosteroids administration.

Mechanism of Action

Corticosteroids, used prudently, exert numerous potent anti-inflammatory properties. Generally, glucocorticoids exert their effects by binding with high affinity to the glucocorticoid cytoplasmic receptor or glucocorticoid receptor (GR). Upon activation, GR forms a homodimer which binds to DNA at consensus sites termed glucocorticoid response elements (GRE) in the 5′-upstream promoter region of glucocorticoid-responsive genes (Barnes 1998; Newton 2000). This binding process leads to the repression of transcription of potent anti-inflammatory or proinflammatory mediators. The transcription of several inflammatory cytokines (IL-1, TNF-a) and chemokines (IL-8, MCP-1) is indirectly inhibited by glucocorticoids. These actions result in the suppression of cellular infiltration, capillary dilation, proliferation of fibroblasts, collagen deposition, and eventually scar formation (Novack 1998). In addition, they increase the synthesis of lipocortins that inhibit the enzyme phospholipase A_2. Inhibition of phospholipase A_2 prevents the conversion of phospholipids to arachidonic acid, a key late-phase mediator in the inflammatory cascade. Nonetheless, corticosteroids also inhibit histamine synthesis by increasing the enzyme histaminase and modulate transcription factors present in mast cell nuclei (Rhen and Cidlowski 2005).

Furthermore, recent evidence suggests the activated corticosteroid-GR complex also elicits nongenomic effects, particularly the inhibition of vasodilation, vascular permeability, and migration of leukocytes (Rhen and Cidlowski 2005; Stahn and Buttgereit 2008). Nonetheless, corticosteroids also mediate their anti-inflammatory activity through membrane-bound GR-mediated nongenomic effects and through direct nonspecific interactions with cellular membranes (Stahn and Buttgereit 2008).

Pharmacokinetics

Limited pharmacokinetic data in intraocular corticosteroids exist, and most studies have been evaluated in rabbit models. Different ocular anatomy likely leads to variable translatable results in humans (Awan et al. 2009). Anatomically, ocular drug delivery can be challenging due to the barriers protecting the human eye. Some of the barriers include drug loss from the ocular surface secondary to lacrimal fluid and tight cornealepithelial cell junctions that decrease drug permeation (Urtti 2006). Data is limited for systemic absorption of ocular steroids; however, rimexolone, when instilled in both eyes every hour for 1 week, resulted in a systemic mean plasma concentration of 150 pg/mL (n = 15) (Vexol® prescribing information). Additionally, loteprednol etabonate studies suggest that about 1 ng/mL reaches systemic circulation (Lotemax® prescribing information). Absorption into the human aqueous humor occurred post 15–30 min, following the instillation of a single drop of dexamethasone and prednisolone sodium phosphate (McGhee 1992).

Drug Information

Please refer to Table 1 (Drug information for ophthalmic steroids in allergic and inflammatory

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Ocular Corticosteroids, Table 1 Drug information for ophthalmic steroids in allergic and inflammatory ocular disorders

Drug name	Common brand name	Strength	Dosing in adults	Dosing in children
Dexamethasone	Decadron®, Maxidex®	1 % ophthalmic solution and suspension	One to two drops in conjunctival sac hourly during the day and every 2 h during the night; reduce to 1 drop every 4 h after favorable response	Safety and effectiveness have not been established in pediatric patients
Fluorometholone	Flarex®, Fluor-Op®, FML®, FML Liquifilm®, FML Forte®	0.1 % ophthalmic ointment, 0.1 % and 0.25 % ophthalmic suspension	Instill one drop of suspension in the conjunctival sac two to four times daily. For ointment, apply 1½ in. ribbon into the conjunctival sac every 4 h initially, then reduce to one to three times daily	2 years and older: Instill one drop of suspension in the conjunctival sac two to four times daily. For ointment, apply 1½ in. ribbon into the conjunctival sac every 4 h initially, then reduce to one to three times daily
Loteprednol etabonate	Alrex®, Lotemax®	0.5 % ophthalmic gel and ointment, 0.2 % and 0.5 % ophthalmic suspension	Instill one or two drops four times daily	Safety and effectiveness have not been established in pediatric patients <18 years of age
Prednisolone acetate	Omnipred®, Pred Forte®, Pred Mild®	1 % ophthalmic solution, 0.12 % and 1 % ophthalmic suspension	Two drops in the eye four times daily	Safety and effectiveness have not been established in pediatric patients
Prednisolone sodium phosphate	Inflamase Mild®, AK-Pred®, Inflamase Forte®	1 % ophthalmic suspension	Instill one or two drops into the conjunctival sac up to every hour during the day and every 2 h at night as necessary, can gradually reduce to one drop three times daily	Safety and effectiveness have not been established in pediatric patients
Rimexolone	Vexol®	1 % ophthalmic suspension	Instill one or two drops four times daily	Safety and effectiveness have not been established in pediatric patients

McEvoy (2006)

ocular disorders) for a summary of brand and generic names, strengths available, and dosing in adults and children.

Safety and Adverse Effects

The glucocorticoid receptor is involved in a plethora of signaling pathways. Long-term usage or high dosages of corticosteroids can result in adverse drug reactions (ADRs) such as increased intraocular pressure (IOP) (McGhee et al. 2002). The mechanism of corticosteroid-induced IOP increase, according to most studies, is implicated by the involvement of the trabecular meshwork (TM) cells and myocilin gene expression. Corticosteroids decrease the outflow of aqueous humor by inhibiting the degradation and/or enhancing the deposition of extracellular matrix material within the TM and/or cross-linking of actin fibers between TM cells (Kersey and Broadway 2006). As a result, the structural changes in the TM lead to corticosteroid-induced ocular hypertension, which can progress to secondary iatrogenic open-angle glaucoma (Clark and Wordinger 2009). Decreased aqueous humor outflow and steroid-induced IOP increase occur when the myocilin, which is a 55-kDa protein, is induced after exposure of TM cells to dexamethasone for 2–3 weeks (Lütjen-Drecoll et al. 1998). A variety of glaucoma phenotypes in both juvenile and adult-onset primary

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open-angle glaucoma occur as a result of different mutations within the myocilin gene, therefore providing further evidence for its role in steroid-induced IOP (Kersey and Broadway 2006).

Loteprednol etabonate (loteprednol) is a unique molecule, as it is considered a "soft" corticosteroid, in that upon the uptake into systemic circulation, it undergoes local metabolism by plasma and tissue esterases into the inactive 17ß-carboxylic acid (Bodor and Buchwald 2005). A meta-analysis conducted by Novack et al. included IOP data from loteprednol development studies where patients were treated with loteprednol, for 28 days or longer. The analysis was composed of a combination of 1,648 healthy volunteers and patients experiencing a variety of ocular inflammatory conditions. The IOP elevations of $\geq$10 mm Hg over baseline were observed in 1.7 % of patients utilizing loteprednol, compared to 0.5 % patients utilizing vehicle and 6.7 % patients utilizing prednisolone acetate (Novack 1998). Nonetheless, Cheng et al.'s conducted meta-analysis of loteprednol IOP data, retrieved from available loteprednol placebo-controlled studies, included a total of 1,660 patients with various ocular conditions. These clinical studies evidenced the IOP elevation rate being 1.7 % in the LE group versus 0.66 % in the placebo group ($p = 0.3$). In the active prednisolone comparator studies, the IOP elevation rate was 5.5 % in the prednisolone group versus 0.8 % in the loteprednol group ($p = 0.05$) (Cheng et al. 2003).

The formation of cataract is another ADR associated with corticosteroid therapy. However, the mechanism of steroid-induced cataract formation is not likely to be related to the downstream effects of GR activation. Various ophthalmic corticosteroids have a ketone group that is located at the C-20 position on the cycloperhydrophenanthrene backbone (Bielory 2008; Bodor and Buchwald 2005). Cataract occurrence involves nonenzymatic formation of Schiff base intermediates between the steroid C-20 ketone group and nucleophilic groups such as ε-amino groups of lysine residues of lens proteins (Manabe et al. 1984). This formation of Schiff base intermediates results in subsequent oxidation of the lens material and development of stable cataract-forming corticosteroid-protein adducts. Cataract formation occurs with long-term glucocorticoid therapy (Manabe et al. 1984).

Rare ophthalmologic complications such as exophthalmos and swelling of the lids and ocular muscles may also occur from glucocorticoids use (Crews 1965). A rare adverse effect of systemic, local, or even topical use of glucocorticoids is central serous chorioretinopathy. Central serous chorioretinopathy is characterized by edema formation that separates the retina from the choroid (Haimovici et al. 2004).

Other adverse effects associated with ocular corticosteroids are reduced wound strength, ocular surface toxicity, exacerbation of microbial infections, delayed epithelial healing, corneal phosphate deposits, keratocyte apoptosis, crystalline keratopathy, reactivation of HSV, lid ptosis, extraocular imbalance, orbital fat atrophy, and dilated pupil.

Drug Interactions

Studies have not been conducted to assess drug interactions with ocular corticosteroids. Corticosteroids, in general, are metabolized by P4503A4 enzymes, which, when administered systemically, will be influenced by drugs that either induce or suppress this oxidative metabolic enzyme. However, because of the decreased dose and systemic absorption of ocular corticosteroids, clinically significant drug interactions are not suspected.

Conclusion

Ocular corticosteroids were introduced to the market and have been utilized in clinical practice since the 1950s. The efficacy and safety of these agents are well documented; however, much of what is currently known regarding the pharmacokinetics in humans is less established. Knowledge of local and systemic adverse effects of ocular corticosteroids is vital since they may

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result in exacerbation of existing disease states. More studies evaluating absorption into the human aqueous humor are warranted to produce new agents with less local adverse effects.

Cross-References

► Topical Corticosteroids

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Oral Allergy Syndrome

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Synonyms

Oral allergy syndrome (OAS); Pollen food allergy syndrome (PFAS)

Definition

Oral allergy syndrome is an adverse reaction that occurs upon ingestion of certain fresh fruits and vegetables in pollen-sensitized individuals.

Introduction

Oral allergy syndrome (OAS), or pollen food allergy syndrome (PFAS), is a condition characterized by an immunoglobulin E (IgE)-mediated immediate hypersensitivity reaction limited to the mouth and throat that occurs after ingestion of fresh fruits and vegetables in pollen-sensitized

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individuals. The causative allergens in these foods share homology to the pollen allergens. Symptoms are short-lived and are most commonly observed with the raw forms of the food (Sampson and Burks 2009).

Historical Background

In 1942, Tuft and Blumstein discussed clinical observations in four adult patients with hay fever who presented with itching of the palate and swelling of the mouth and throat after consuming different raw fruits (Tuft and Blumstein 1942). The patients indicated that their symptoms were more noticeable in the pollen season. Skin prick testing was positive to freshly extracted fruit juice and negative to stock extracts of these foods. At that time, Tuft and Blumstein demonstrated two important concepts: the presence of a labile antigen in fresh fruit extracts and the destruction of this antigen by heat. The relationship between plant antigens and pollinosis was not identified until the late 1970s when the first antigenic correlation among birch, apple, potato, and hazelnut was realized (Anderson and Lowenstein 1978). This clinical entity was denominated as "Oral Allergy Syndrome" in 1987 (Amlot et al. 1987).

Epidemiology/Prevalence

The true prevalence of OAS in the United States has not been determined. However, it is probably the most common type of food allergy in adults. This speculation is because of its relationship with allergic rhinitis, which affects 10–30% of adults and 40% of children (Wallace et al. 2008). Also, OAS is on the rise and this is likely due to the fact that sensitization to aeroallergens has almost doubled over the past two decades (Sicherer 2001).

Sensitization to tree pollen, namely, birch pollen, is associated with the highest rates of OAS. Allergy to grass and weed pollen is less commonly associated with OAS. In one study, pollen-sensitized individuals were evaluated for OAS through supervised oral food challenges. The probability of a clinical reaction to pollen-related foods in this pollen-sensitized group was 24% when sensitized to birch, 10% when sensitized to mugwort, and 4% when sensitized to grass (Osterballe et al. 2005). Interestingly 52% of subjects allergic to three pollens (birch + grass + mugwort) reacted to related foods indicating that individuals sensitized to multiple pollens are much more likely to be affected by OAS. Moreover, the odds ratio of a clinical reaction to pollen-related fruits and vegetables was up to four times higher among those with symptoms of pollinosis (nasal, ocular, and respiratory symptoms of pollen allergy), indicating that patients with pollen-induced symptoms are at a higher risk than patients who are sensitized and have no symptoms (Osterballe et al. 2005).

Pathogenesis

Fruits and vegetable allergens share a high degree of homology with pollens and this explains the cross-reactivity observed clinically (Kazemi-Shirazi et al. 2000). Sensitization to pollen is believed to be the initial event leading to the generation of IgE antibodies that can cross-react with homologous food allergens (Valenta and Kraft 1996). After oral contact with the related food, these IgE molecules recognize the homologous plant proteins in the food and cause local release of inflammatory mediators triggering the symptoms observed in OAS. Allergens are subsequently destroyed in the stomach and no further reactions are typically noted. This mechanism of food allergy (class 2 food allergy) is different from class 1 food allergy where sensitization occurs throughout the gastrointestinal tract from a protein allergen resistant to gastric digestion.

Allergens, Associations, and Foods

The conformational IgE-binding epitopes implicated in oral allergy syndrome are sensitive to

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heat and digestive enzymes, which is in contrast to allergens causing type 1 food allergy (which are resistant to heat and digestion), and have a high potential to cause systemic symptoms.

OAS is caused by a variety of plant proteins, especially pathogenesis-related (PR) proteins that cross-react with airborne allergens. These proteins are involved in plant defense and resistance to stress in their environment (Nash and Burks 2007). An example would be Mal d1 (the major apple allergen) and Bet v1 (the major birch allergen). Both share some homology and are known to cross react. Also, Bet v2 (birch pollen profilin) cross reacts with profilins found in pear (Pyr c4) and celery (Api g4) (Sampson and Burks 2009).

Patients allergic to birch pollen may develop oral symptoms after ingestion of fresh apples, apricots, potatoes, hazelnuts, carrots, celery, kiwi, cherries, pears, walnuts, and other foods (Sloane and Sheffer 2001).

Patients allergic to ragweed pollen may react to bananas and fresh melons, whereas patients allergic to mugwort may react to apples, melons, and celery (Sloane and Sheffer 2001).

Clinical Manifestations

IgE-mediated allergic symptoms are typically restricted to the oral mucosa and include itching, tingling, and erythema or angioedema of the lips, tongue, oropharynx, and throat that is sometimes accompanied by a sensation of throat closing (Sampson and Burks 2009). Symptoms occur within a few minutes after ingestion of the culprit fruit or vegetable and are short-lived (Sloane and Sheffer 2001).

Also, symptoms may vary throughout the year and typically increase during the specific pollen season due to seasonal peaking of related pollen IgE levels (Sampson and Burks 2009; Sussman et al. 2010).

Although OAS symptoms are typically mild, there are reports of severe reactions (Sicherer 2001). Certain foods such as tree nuts have been associated with higher rates of systemic reactions.

Diagnosis

The diagnosis is almost entirely based on the patient's medical history. History of respiratory allergies (hay fever and/or asthma during a specific pollen season) and symptoms consistent with OAS are enough to make a diagnosis of OAS in most cases. Diagnosis can be confirmed with positive prick-prick skin tests with the implicated fresh fruits and vegetables in patients with allergic rhinitis. This procedure is done by pricking the fruit with the lancet and then immediately using the same lancet for the skin prick. Skin prick tests with commercial extracts are often negative since the responsible allergen is often destroyed during the manufacturing process (Ortolani et al. 1989).

Systemic reactions such as total body hives, wheezing, and anaphylaxis are rare in OAS. In these cases, patients should be worked up for a more serious IgE-mediated food allergy.

Oral food challenges may have to be considered when the history cannot provide enough information regarding the responsible food or is not typical of OAS (symptoms persisting for hours, symptoms with cooked food) or when sensitization to either pollens or respective foods has not been proven. In OAS, the oral food challenge is negative with cooked food.

Management

There are no established guidelines for the management of OAS and dietary avoidance of the raw culprit food is the mainstay of management. Since many patients can tolerate cooked, microwaved, partially ripe or peeled fruits, consumption of these forms may be allowed unless systemic reactions have been previously reported (Konstantinou and Grattan 2008).

Although it is rare for patients with OAS to develop systemic reactions and anaphylaxis, consideration could be given to prescribing autoinjectible epinephrine (Lieberman et al. 2010).

Since pollen allergens are responsible for the cross reactivity with food allergens in OAS,

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sublingual and subcutaneous immunotherapy have been tried therapeutically and results vary in their outcome (Webber and England 2010).

Conclusion

OAS describes an allergic reaction that is localized to the oropharynx and occurs upon ingestion of certain fresh fruits and vegetables in pollen-sensitized individuals. The culprit allergen is rapidly inactivated by digestion and cooking. Symptoms usually resolve promptly when food is swallowed. Diagnosis is based almost entirely on medical history and a positive prick-prick test. The mainstay of management is avoidance of the raw culprit food. Immunotherapy for pollen allergy is beneficial to a subset of patients with OAS.

Cross-References

- ▶ Diagnostic Components: Allergen for In Vivo (Skin Testing, Immunotherapy) and In Vitro (Serology) IgE Antibody Testing
- ▶ Diagnostic Food Challenges
- ▶ Epidemiology of Food Allergy
- ▶ Food Allergens
- ▶ Food Allergies, Diagnostic Testing
- ▶ Food Allergy and its Future Treatment
- ▶ Food Allergy, Overview
- ▶ Immunotherapy, Mechanisms

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Oral Antihistamines

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Synonyms

H1 blocker; Histamine antagonist

Definition

Allergic rhinitis is a pervasive disease in the USA, in which histamine plays a key role in the pathophysiology (Benninger et al. 2010). Multiple histamine receptors are recognized, and histamine 1 (H1) receptors are the most prominently associated with allergic symptoms. Blocking H1 receptors has demonstrated a decrease in the symptoms associated with allergic rhinitis (rhinorrhea, sneezing, and itching). Antihistamines are a mainstay in the treatment of allergic rhinitis, and their use has been associated with improved quality of life (Wallace et al. 2008). Antihistamines have been used in the treatment of allergic rhinitis for over 60 years.

Mechanism of Action

Histamine (an autocoid amine synthesized from histidine) is primarily stored in mast cells. Mast cells undergo degranulation when its high-affinity receptors (FcεRI) are bound and cross-linked by IgE-bound antigens. Once histamine is released, it will initiate an allergic response when they bind to and activate H1 receptors. After binding and activation, second messenger gated calcium channels to release calcium from the smooth endoplasmic reticulum (ER) and the sarcoplasmic reticulum (SR). The increase in cytosolic calcium triggers smooth muscle constriction in the bronchioles and gastrointestinal tract. H1 receptors are G protein-coupled receptors, which are often found in smooth muscles, endothelium, and central nervous system tissue. Other histamine receptors are recognized (H2 through H4) but are beyond the scope of this subject.

H1-antihistamines are inverse agonists of H1 receptors, blocking initial steps in the allergic response (Leurs et al. 2002). Prior evidence suggested that antihistamines were competitive inhibitors of H1 receptors, preventing H1 receptors to bind histamine. However, when H1 receptors are free of substrate, they exist in equilibrium between an inactive confirmation and an active confirmation.

1st-Generation Antihistamines

Antihistamines are classified into three generations. First-generation (or classic) antihistamines are distinguishable due to their ability to cross the blood–brain barrier. They are neutral, lipophilic compounds at physiological pH (Goldberg et al. 1987). Evidence indicates that 1st-generation antihistamines show no affinity for P-glycoprotein (Chishty et al. 2001) (PgP), a class of efflux transporters which influence the distribution and elimination of many clinically relevant medications (e.g., amoxicillin, atorvastatin, sertraline). The lack of affinity for PgP coupled with lipophilicity, the 1st-generation antihistamines easily transport across the BBB in to the CSF. Antihistamines will thus cause impairments in cognitive function, memory, psychomotor performance, as well as sedation. The sedative property of antihistamines is profound: they are the primary ingredient in popular OTC sleep aid medications, and operation of a vehicle under the influence of 1st-generation antihistamines is a considered ground for DUI in some states (Bender et al. 2003). The CNS effects of alcohol and other CNS depressants may be potentiated in the presence of sedative antihistamines (Bender et al. 2003). Paradoxical excitation of the CNS may also occur in some patients taking 1st-generation antihistamines and in extreme cases is a sign of toxicity.

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First-generation antihistamines also possess significant anticholinergic properties (and some adrenergic, dopaminergic, and serotonergic properties), and the said properties may be effective in preventing/treating motion sickness. Table 1 lists common antihistamines and their doses.

Tricyclic antihistamines, including cyproheptadine and promethazine, are structurally similar to tricyclic antidepressants (TCAs). Doxepin is classified as a TCA but also has potent antihistamine and anticholinergic activity (Richelson 1979). TCAs have fallen out of favor as a therapeutic option in modern pharmacotherapy due to their prevalent side effects. Meclizine, dimenhydrinate, and promethazine are useful in nausea and vomiting due to their central antiemetic effects. Promethazine also has sedative-hypnotic properties and may potentiate other analgesic drugs. Table 2 lists doxepin and other tricyclic antihistamines used in treating allergic rhinitis.

2nd-Generation Antihistamines

The distinct differences between 1st- and 2nd-generation antihistamines are their lipophilicity and affinity for PgP. The 2nd-generation antihistamines are larger molecules, less lipophilic, ionized at physiological pH, and have a higher affinity for PgP and albumin.

These properties diminish the ability of the 2nd generation to cross the BBB and elicit less associated adverse effects more commonly seen with the 1st generation. Regardless, cetirizine, a 2nd-generation antihistamine, demonstrates some sedation in the population. Cetirizine has a similar (and additive) effect on driving performance when compared to alcohol (Bender et al. 2003). Table 3 lists antihistamines in the 2nd-generation class.

3rd-Generation Antihistamines

Further structural changes, including enantiomer selection or implementation of an active metabolite, were the developmental aims of the 3rd-generation antihistamines. By doing so, the intent was to further reduce the untoward adverse effects (primarily sedation) seen in 2nd-generation antihistamines.

Levocetirizine is the R-isomer of cetirizine, and by removal of the ethyl acetate group, desloratadine is the active metabolite of loratadine. Desloratadine demonstrates a higher affinity for the H1 receptor than levocetirizine and fexofenadine (Devillier et al. 2008). Currently the 3rd generation is prescription only in the USA. Table 4 lists antihistamines in the 3rd-generation class.

Pharmacokinetics

Antihistamines are well absorbed from the gastrointestinal (GI) tract. Antihistamines reach peak plasma concentrations within 1–3 h. The 2nd- and 3rd-generation antihistamines have a longer duration of action. First-generation antihistamines are often dosed every 4–6 h, whereas 2nd- and 3rd-generation antihistamines are often dosed every 12–24 h.

Generally, antihistamines are subject to hepatic metabolism, with both magnitude and prevalence being greater in the earlier generations. Cetirizine, levocetirizine, and fexofenadine do not undergo extensive hepatic metabolism (Motala 2009). The majority of 1st-generation antihistamines (diphenhydramine, chlorpheniramine, and hydroxyzine) are inhibitors and substrates of CYP2D6 and substrates of CYP3A4 (Sharma and Hamelin 2003; Guengerich 2006).

In the late 1990s, terfenadine became a highlight in clinically relevant drug interactions with the CYP P450 metabolic system. Terfenadine (2nd-generation antihistamine) is a substrate for P450 3A4, and when combined with a known inhibitor (erythromycin), the untoward effect of torsades de pointes surfaces (Woosly et al. 1993). This deadly cardiovascular adverse effect precipitated the removal of terfenadine (Seldane®) from the US market in 1997 (FDA Talk Paper 1997). Fexofenadine is the active metabolite of terfenadine and is safely

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Oral Antihistamines, Table 1 First-generation antihistamines approved for allergic rhinitis

Generic name	Brand name	Dosage for allergic symptoms/allergic rhinitis	Chemical class
Diphenhydramine	Benadryl®	*Pediatrics*	Ethanolamine
	Q-Dryl	2–6 y/o:	
	Banophen	6.25 mg/dose every 4–6 h	
	Diphedryl	7–12 y/o:	
	Diphenhist	12.5–25 mg/dose every 4–6 h	
	Dytan	*Adults*	
		25–50 mg/dose every 4–6 h	
		Geriatrics	
		25 mg/dose every 8–12 h	
Brompheniramine	Dimetapp®	*Pediatrics* (6–12 year)	Alkylamine
	Bromax®	< 6 y/o, IR:	
	LoHist-12®	0.125 mg/kg/dose every 6 h	
	Respa-BR®	Maximum dose: 6–8 mg/day	
	VaZol®	2–6 y/o, ER:	
	J-Tan®	2 mg/dose every 12 h	
	TanaCof-XR	6–12 y/o, IR:	
		2–4 mg/dose every 6–8 h	
		Maximum dose 12–16 mg/day	
		6–12 y/o, ER:	
		4 mg/dose every 12 h	
		Adults	
		IR:	
		4–8 mg/dose every 6 h	
		Maximum dose: 24 mg/day	
		ER:	
		6–12 mg/dose every 12 h	
		Maximum dose: 24 mg/day	
Chlorpheniramine	Chlor-Trimeton®	*Pediatrics*	Alkylamine
	ller-Chlor	2–6 y/o:	
	ED Chlor-Tan	1 mg/dose every 4–6 h	
	Teldrin HBP	7–12 y/o:	
	AHIST	2 mg/dose every 4–6 h	
		Adults	
		4 mg/dose every 4–6 h	
		Geriatrics	
		4 mg/dose every 12–24 h	
Cyproheptadine	Periactin®	*Pediatrics*	Piperidine
		2–6 y/o:	
		2 mg/dose every 8–12 h	
		7–14 y/o:	
		4 mg/dose every 8–12 h	
		Adults	
		4–20 mg/day over 3 doses	

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Oral Antihistamines, Table 2 Mixed-effect antihistamines used for allergic rhinitis

Generic name	Brand name	Dosage for allergic symptoms/allergic rhinitis	Chemical class
Hydroxyzine (Piperazine)	Vistaril®	*Pediatrics*	Piperazine
	Atarax®	2 mg/kg/day every 6–8 h	
		15 mg/m2/day in divided doses	
		Adults	
		25 mg/dose every 6–8 h	
Promethazine	Avomine®	*Pediatrics*	Phenothiazine
	Prothiazine®	2–12 y/o	
	Phenergan®	6.25–12.5 mg/dose every 8 h	
		Adults	
		12.5 mg/dose every 8 h	
		Administer before meals	
		Geriatrics	
		6.25–12.5 mg/dose every 8 h	
		Administer before meals	
Dimenhydrinate	Dramamine®	*Pediatrics*	Ethanolamine
	Driminate®	2–5 y/o:	
	TripTone®	12.5 mg/dose every 6–8 h	
		Maximum dose: 75 mg/day	
		6–12 y/o:	
		25–50 mg/dose every 6–8 h	
		Maximum dose: 150 mg/day	
		Adults	
		50–100 mg/dose every 4–6 h	
		Maximum dose: 400 mg/day	
Doxepin	Silenor®	*Adults*	Tricyclic dibenzoxepin
		Depression/anxiety:	
		Initially 25–150 mg/day in 2–3 divided dose	
		May gradually increase to 300 mg/day	
		Maximum single dose: 150 mg	
		Insomnia:	
		3–6 mg/dose 30 min prior to bedtime	
		Geriatrics	
		Insomnia:	
		3 mg/dose 30 min prior to bedtime	
		Maximum dose 6 mg/day	
Meclizine	Antivert®	*Adults* (12 y/o or older)	Piperazine
	Bonine	Motion sickness: 25–50 mg 1 h prior to travel	
	Medivert	Repeat dose every 24 h if needed	
	Meni-D	Vertigo: 25–100 mg in divided doses	

used in the treatment of allergic diseases. Other antihistamines are substrates for 3A4 (loratadine) and PgP (loratadine, fexofenadine), but clinically relevant drug-drug interactions have not been observed (Kosoglou et al. 2000; Yasui-Furukori et al. 2005).

Half-life, duration of action, and dosing frequency vary among antihistamines. This may be due to differences in tissue to plasma concentrations and active metabolite formation. The 1st generation antihistamine requires frequent dosing, whereas the newer generations are

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Oral Antihistamines, Table 3 List of 2nd-generation antihistamines

Generic	Brand name	Dosage	Chemical class
Cetirizine	Zyrtec®	*Pediatrics*	Piperazine
		7–12 y/o: 5–10 mg once a day	
		Adults	
		5–10 mg once a day	
Loratadine	Claritin®	*Pediatrics*	Piperidine
	Alavert®	2–5 y/o: 5 mg once a day	
		6–12 y/o: 10 mg once a day	
		Adults	
		5–10 mg once a day	
Fexofenadine	Allegra®	*Pediatrics*	Piperidine
		2–11 y/o: 30 mg/dose every 12 h	
		Adults	
		60 mg/dose every 12 h or 180 mg once daily	
		Geriatrics	
		Adjust for renal impairments	
Acrivastine	Semprex-D®	*Adults*	Alkylamine
		8–60 mg/dose every 6 h	
		Not recommended in renal-impaired patients	

Oral Antihistamines, Table 4 List of 3rd-generation antihistamines

Generic	Brand name	Dosage	Chemical class
Levocetirizine	Xyzal®	*Pediatrics*	Piperazine
		7–11 y/o: 2.5 mg once a day	
		Adults	
		5 mg once a day	
Desloratadine	Clarinex®	*Pediatrics*	Piperidine
		6–12 month: 1 mg once a day (oral solution)	
		1–5 y/o: 1.25 mg once a day (oral solution)	
		6–11 y/o: 2.5 mg once a day	
		Adults	
		5 mg once a day	

dosed mostly once daily. Acrivastine is a notable exception among the 2nd generation, which is dosed 4–6 times a day.

Combinations

Pseudoephedrine or phenylephrine is often combined with various antihistamines to serve as a decongestant. They also help to mask the drowsiness antihistamines can cause. In addition to the side effects associated with antihistamines, these can also cause an increase in blood pressure.

Conclusions

Antihistamines are heavily utilized for the treatment of allergic rhinitis. The 1st-generation

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agents are effective in reducing the symptoms of allergic rhinitis, but their use is limited due to sedative and anticholinergic side effects. However, these side effects often lead to the use of first-generation antihistamines for alternative uses. The 2nd-generation agents are more selective for the H1 receptor. Their penetration of the BBB is minimal in comparison to 1st-generation antihistamines. Clinically, this resulted in an improved side effect profile. Of the 2nd-generation agents, cetirizine is the only agent associated with significant sedative effects. Loratadine has the higher potential of drug-drug interactions among the 2nd-generation agents. Patients should consult their doctor or pharmacist before taking loratadine. The 3rd-generation antihistamines consist of the active enantiomer or metabolite of 2nd-generation agents to decrease the side effects. However, 3rd-generation antihistamines are more costly than 2nd-generation antihistamines and are currently prescribed only in the USA.

Cross-References

- Intranasal Antihistamines
- Ocular Antihistamines
- Oral Corticosteroids
- Oral Decongestants
- Oral Mast Cell Stabilizers
- Topical Antihistamines

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Oral Corticosteroids

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Synonyms

Glucocorticoids; Oral steroids; Systemic corticosteroids

Definition

Corticosteroids are hormones secreted by the adrenal cortex or are synthetic analogs of these hormones. They are typically classified as glucocorticoids or mineralocorticoids. Glucocorticoids are widely used for the suppression of inflammation in patients with inflammatory, allergic, immunological disorders, all of which are associated with increased expression of inflammatory genes (Barnes 1998). They are further classified based on their potency and duration of action (Table 1). A short course (5–7 days) of oral corticosteroids may be warranted in the setting of allergies for cases of severe or intractable nasal symptoms of allergic rhinitis and nasal obstruction (Scadding et al. 2008).

Mechanism of Action

Glucocorticoids exert their effects by binding with high affinity to the glucocorticoid cytoplasmic receptor or glucocorticoid receptor (GR). Upon activation, GR forms a homodimer which binds to DNA at consensus sites termed glucocorticoid response elements (GRE) in the 5′-upstream promoter region of glucocorticoid-responsive genes (Barnes 1998).

This binding process leads to the repression of transcription of potent anti-inflammatory or proinflammatory mediators. The transcription of several inflammatory cytokines (IL-1, TNF-α) and chemokines (IL-8, MCP-1) are indirectly inhibited by glucocorticoids. In allergic inflammation, the expression of cytokines IL-4 (critical for IgE synthesis) and IL-5 (critical for eosinophilic inflammation) is also inhibited by glucocorticoids. A reduction of expression of adhesion molecules on endothelial cells occurs secondary to the downregulation of cytokines, preventing the adhesion and transmigration of leukocytes to the site of inflammation. The end result of these processes leads to edematous diminution (Barnes 1998).

Pharmacokinetics

Absorption/Distribution

Oral glucocorticoids are absorbed well and have a bioavailability between 60 % and 100 % (Czock et al. 2005). Distribution of glucocorticoids differs to the extent in which they are protein bound. For example, hydrocortisone has a high binding affinity to transcortin (i.e., corticosteroid-binding globulin) and albumin (McEvoy 2006). Prednisolone has a higher affinity for transcortin than other synthetic glucocorticoids; it has a tenfold higher binding affinity to transcortin than prednisone (Czock et al. 2005). Both hydrocortisone and prednisolone exhibit nonlinear pharmacokinetics. When plasma concentrations of prednisolone reach between 200 and 800 μg/L, the protein binding decreases in a nonlinear fashion from 95 % to 60–70 % (Czock et al. 2005). Methylprednisolone and dexamethasone bind exclusively to albumin and have no affinity for transcortin.

Metabolism/Elimination

Synthetic glucocorticoids having a ketone group at the C-11 position (e.g., cortisone, prednisone) requires 11-β- hydroxysteroid dehydrogenase type 1 to reduce it to an active form. This activity mainly occurs in the liver. In contrast, 11-β-hydroxysteroid dehydrogenase type 2 catalyzes the conversion of cortisol back to cortisone. Cortisone formed in the liver is reduced and conjugated to tetrahydrocortisone glucuronide

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Oral Corticosteroids, Table 1 Relative potencies of glucocorticoids: adapted with permission from McGraw-Hill

	Anti-inflammatory	Equivalent potency	Approximate half-life (plasma)	Duration of action	Sodium-retaining	
Glucocorticoid	Potency	Milligram	Minutes	hours	Potency	Classification
Cortisone	0.8	25	30	8–12	2	Short acting
Hydrocortisone	1	20	90	8–12	2	Short acting
Prednisone	3.5	5	60	12–36	1	Intermediate acting
Prednisolone	4	5	200	12–36	1	Intermediate acting
Triamcinolone	5	4	200	12–36	0	Intermediate acting
Methylprednisolone	5	4	180	12–36	0	Intermediate acting
Betamethasone	25	0.6	100–300	36–54	0	Long acting
Dexamethasone	30	0.75	100–300	36–54	0	Long acting

(Schimmer and Funder 2011). These compounds enter into circulation and are rapidly excreted by the kidneys.

Drug Interactions

Glucocorticoids are metabolized in the liver mainly by the cytochrome P450 (CYP) enzyme 3A4. Administering glucocorticoids with CYP 3A4 inducers, such as barbiturates, phenytoin, carbamazepine, and rifampin, will increase the clearance of glucocorticoids. In contrast, co-administration with CYP 3A4 inhibitors, such as azole antifungals and macrolide antibiotics, will decrease the clearance and increase the half-life of glucocortiocoids (Czock et al. 2005). Additionally, *in vitro* studies have demonstrated that cortisol, prednisolone, methylprednisolone, and dexamethasone are substrates for p-glycoprotein (PGP) membrane transporters; thus, co-administration of PGP inhibitors (e.g., cyclosporine-A, verapamil, protease inhibitors) will likely increase the concentration of glucocorticoids (Yates et al. 2003).

Adverse Effects

Glucocorticoid toxicity is generally associated with both the average dose and cumulative duration of therapy, despite the inability to establish a "threshold" dose or duration for most adverse effects (Da Silva et al. 2006). Several retrospective studies evidenced that chronic use of glucocorticoids in small doses leads to various significant adverse effects, correlating the risk to be both dose and time dependent (Saag et al. 1994). Nonetheless, data from four randomized trials involving 568 patients with rheumatoid arthritis were given low-dose glucocorticoids, such as prednisone 5–10 mg/day. Patients were followed for 2 years. According to these trials, little evidence regarding the degree of risk from low-dose glucocorticoids was found, in addition to an insignificant number of adverse effects related to low-dose glucocorticoid use (Saag et al. 1994).

Oral glucocorticoids may be given on a short-term basis with minimal toxicity. The incidence of serious adverse effects increases with higher doses involved with chronic glucocorticoid therapy.

Infection and immune response: Corticosteroids are immunosuppressive agents that have an effect on innate and acquired immunity. The increase in the risk of infection is dependent on the dose of glucocorticoids. The intensity of therapy influences the infection risk secondary to dose-dependent inhibitory effects on phagocytic cell function (Sakuma et al. 2005). Common bacterial, viral, and fungal pathogens

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may occur with greater frequency in a dose-dependent manner during glucocorticoid therapy.

Musculoskeletal Effects: Protein catabolism, myalgia, muscle atrophy or myasthenia, and poor wound healing are adverse effects associated with oral corticosteroids. In addition, protein matrix of the bone may atrophy, resulting in vertebral compression fractures, fractures of the long bones, and/or osteoporosis. These adverse effects may be critical in postmenopausal women, patients of advanced age, or those who are debilitated (Kumagai et al. 2005).

Ocular Effects: Chronic administration of systemic corticosteroids may result in cataracts or glaucoma (Tripathi et al. 1999).

Endocrine Effects: Prolonged therapeutic use of oral corticosteroids may produce various endocrine disorders including Cushingoid syndrome. This syndrome is characterized by adrenal insufficiency, dorsocervical fat pad, weight gain with central obesity, moon facies, hyperglycemia, glycosuria, and hypogonadism (Huscher et al. 2009). Additionally, suppression of the adrenocorticotropic hormone (ACTH) release from the pituitary gland leads to decreased secretion of endogenous corticosteroids, occurring secondary to oral corticosteroids in pharmacologic doses. The degree of adrenal suppression and duration is variable among patients, as it is dependent upon dose, frequency, time of administration, and duration of therapy (Berg and Nilsson 1996).

Dermatologic Effects: Various adverse dermatologic effects are attributable to oral corticosteroids use including skin atrophy and thinning; impaired wound healing; acne; hirsutism; easy bruising; and striae of abdomen, thighs, and axillas (Fardet et al. 2007).

Gastrointestinal Effects: Peptic ulceration is an occasional adverse effect associated with oral corticosteroid as a sole therapy. However, the risk of peptic ulcer rises significantly when used concurrently with NSAIDs (Piper et al. 1991). The insidious nature of the development, reactivation, perforation, and/or hemorrhage of these ulcers categorize these adverse effects as a critical therapeutic problem. Other adverse gastrointestinal effects include increased appetite, weight gain, nausea, vomiting, anorexia, abdominal distention, gastric irritation, pancreatitis, and ulcerative esophagitis (Conn and Poynard 1994).

Nervous System Effects: Chronic administration of systemic corticosteroids may lead to behavioral changes secondary to their usage and may take various forms, including depression, insomnia, nervousness, delirium, euphoria, anxiety, personality changes, mania, psychoses, and even suicidal tendencies (Fardet et al. 2012). Previously diagnosed patients with neuropsychiatric disorder may be at an increased risk for developing behavioral disturbances, following glucocorticoid therapy. Meanwhile, the absence of a history of psychiatric illness does not guarantee elimination of the occurrence of psychosis during oral corticosteroid therapy. Other neurological adverse effects include vertigo, headache, and seizures (Brown and Chandler 2001).

Other adverse effects associated with chronic use of oral corticosteroids include renal calculi; polyuria; hypokalemic alkalosis; sodium retention with resultant edema; growth retardation in children; and hypertension (Panoulas et al. 2008).

Clinical Efficacy

Oral corticosteroids are recommended for short-term use in patients with severe intractable nasal symptoms or nasal obstruction associated with allergic rhinitis (Scadding et al. 2008). Due to short- and long-term adverse effects (described above), intranasal corticosteroids are recommended for long-term use in the setting of allergic rhinitis (Karaki et al. 2013). The first and only study to compare intranasal and oral corticosteroids for seasonal allergic rhinitis (SAR) evaluated the efficacy of intranasal corticosteroid mometasone furoate (Nasonex®) with betamethasone oral tablets for seasonal allergic rhinitis treatment (Karaki et al. 2013). This was an open label study for patients with intermediate to severe symptoms of SAR and allocated patients to either of three treatment groups: loratadine (Claritin®) 10 mg daily (n = 23), mometasone furoate 200 mcg (100 mcg in each nostril) once daily plus loratadine (n = 23),

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or betamethasone 0.25 mg by mouth twice daily plus loratadine (n = 24). The treatment arms were provided for 1 week, and then patients completed questionnaires to measure efficacy. Both the mometasone and betamethasone treatment arms provided a significant reduction over loratadine alone in individual and total scores for sneezing, nasal obstruction, nasal itching, and watery nasal discharge ($p < 0.05$). The authors noted no major adverse events; however, the study was over a 1-week period. The demonstrated equivalent effectiveness of intranasal corticosteroids with oral glucocorticoids lends support to the guideline recommendations to use the oral agents only for severe cases due to the known short- and long-term adverse effects.

Conclusion

Corticosteroids have a wide variety of uses ranging from endocrine disorders to allergic, immunologic, and inflammatory disorders. Oral corticosteroids are recommended only for a short course of 5–7 day for severe cases of allergic rhinitis. Due to the wide variety of use, healthcare professionals need to be aware of the numerous adverse effects that occur with both acute and chronic usage. Additionally, because approximately half of the drugs on the market undergo biotransformation through CYP 3A4, checking for drug interactions with glucocorticoids is imperative.

Cross-References

- ▶ Allergen Immunotherapy, Overview
- ▶ Immunotherapy for Asthma
- ▶ Immunotherapy, Mechanisms
- ▶ Safety of Immunotherapy

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Oral Decongestants

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Synonyms

Alpha-receptor agonists; Oral sympathomimetics; Sympathomimetic decongestants; Systemic decongestants

Definition

Oral decongestants are used to temporarily relieve nasal congestion associated with allergic/nonallergic rhinitis and rhinosinusitis (Gwaltney et al. 1995; Tran et al. 2011). Agents in this class that can be found in both prescription and nonprescription medication include pseudoephedrine and phenylephrine. Despite the efficacy of oral decongestants, these products are becoming more difficult to obtain due to the associated risks. A once popular weight loss agent and decongestant, phenylpropanolamine, was removed from the US market due to increased risk of hemorrhagic stroke (Kernan et al. 2000). Pseudoephedrine was once very accessible over the counter, but now has been moved behind the counter in pharmacies because it is used in the synthesis of methamphetamine. In 2006, the US congress passed the *Combat Methamphetamine Epidemic Act of 2005*. This act prohibits the daily sale of more than 3.6 g of the base product and no more than 9 g per 30 days per individual. The seller pharmacy must maintain a logbook of each sale and document the buyer's name, address, date, and time of sale and obtain the buyer's signature. Ephedra (ma huang) is an herbal supplement with sympathomimetic properties that has been used for treatment of common cold and allergic rhinitis; however, the Federal Drug Administration banned the sale of dietary supplements containing this active ingredient due to the risk of heart attack, stroke seizure, and even death (Haller and Benowitz 2000).

Mechanism of Action

Blood vessels in the venous sinuses normally remain constricted due to the constitutive sympathetic release of norepinephrine from adrenergic neurons in the nasal passage (Eccles 2000). Swelling caused by vasodilation of these tissues can partially or completely obstruct the nasal passage. Oral decongestants are sympathomimetic agents (adrenergic agonists) which imitate the effects or alter the release of norepinephrine and epinephrine and act on alpha-1 receptors locally in the venous sinuses and systemically. This stimulation of the sympathetic system causes vasoconstriction of sinus blood vessels, reducing the size of the venous sinuses and, consequently, airflow resistance (Corey et al. 2000). Phenylephrine is an alpha-1 agonist but at higher concentrations can activate beta receptors (Westfall and Westfall 2011). Pseudoephedrine is an indirect-acting decongestant, which displaces norepinephrine from the storage vessels in presynaptic neuronal junctions (Tietze 2002). Table 1 shows the most commonly used oral decongestants and their dosing in the adult and pediatric population.

Pharmacokinetics

Pseudoephedrine is readily absorbed in the gastrointestinal tract. A maximum concentration of 180 ng/mL was achieved in 1.39 h after administration of 60 mg of liquid or an immediate release tablet, and a concentration of 422 ng/mL was observed in 1.97 h after administration of a 120 mg dose of pseudoephedrine. The twice daily dose tablet had a T_{max} between 3.8 and 6.1 h and the 24 h tablet had a T_{max} of 11.87 h (Kanfer et al. 1993). The onset of action is seen in

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Oral Decongestants, Table 1 Drug information for oral decongestants in nasal congestion

Drug name	Strength	Dosing in adults and children ≥ 12	Dosing in adolescents and children 6 to <12	Dosing in adolescents and children 2 to <6
Phenylephrine	10 mg	10 mg every 4 h as needed	5 mg every 4 h	2.5 mg every 4 h
		Maximum: 60 mg/day	Maximum: 30 mg/day	Maximum 15 mg/day
Pseudoephedrine	Immediate release tablet: 30 mg, 60 mg	30–60 mg every 4–6 h. Sustained release 12 h tablet: 120 mg every 12 h	30 mg every 6 h	15 mg every 4–6 h
	Sustained release 12 h: 120 mg	Sustained release 24 h tablet: 240 mg every 24 h	Maximum: 120 mg/24 h	
	24 h: 240 mg	Maximum: 240 mg/day		Maximum: 60 mg/day

McEvoy (2006)

30 min (Chua et al. 1989). Phenylephrine has a bioavailability of 38 %. Maximum concentrations of phenylephrine are variable, ranging from 0.9 to 298 ng/mL with a T_{max} reported between 45 min and 2 h after oral administration.

The volume of distribution (V_d) in adults for pseudoephedrine is 2.64–3.51 L/kg, and approximately 0.5 % is excreted in breast milk over 24 h (Kanfer et al. 1993). The V_d for phenylephrine is variable; initially the volume of distribution is 26–61 L, but at steady state, the V_d increases to 184–543 L (Kanfer et al. 1993). Excretion of phenylephrine into breast milk is minimal but has been shown to reduce mean milk volume by 24 % (Aljazaf et al. 2003; Kanfer et al. 1993).

A small portion of pseudoephedrine (<1 %) is eliminated via hepatic metabolism. An active metabolite, norpseudoephedrine, is formed from N-demethylation (Chua et al. 1989; Kanfer et al. 1993). After 24 h post administration, 43–96 % of the parent compound can be recovered in the urine. Norpseudoephedrine can be recovered in the urine 48 h after dosing and pseudoephedrine can be found in the urine up to 72 h after administration (Kanfer et al. 1993).

Phenylephrine undergoes sulfation and oxidation via monoamine oxidase in the intestinal walls. Phenylephrine and its metabolites are eliminated almost exclusively in the urine; only 2.6 % of the oral drug and 16.6 % of intravenous drug are excreted unchanged (Kanfer et al. 1993). Recovery of the parent compound and metabolite was between 80 % and 86 % after 48 h post administration (Kanfer et al. 1993).

Drug Information

Please refer to Table 1, Drug information for oral decongestants in nasal congestion, for a summary of strengths available and dosing in adults and children. Table 2, List of phenylephrine and pseudoephedrine products, provides a list of the specific products available in the US market.

Drug Interactions

Use of oral decongestants is contraindicated within 14 days of monoamine oxidase inhibitor (MAOI) administration because this can precipitate hypertensive crisis (Kanfer et al. 1993; Woo 2011). Additionally, beta blockers increase the sympathomimetic effects; therefore, patients taking beta-adrenergic receptor antagonists should avoid oral decongestants (Woo 2011).

Clinical Safety and Efficacy

In a double-blinded, placebo-controlled study, 54 participants with the common cold for 5 days or less were investigated to assess the efficacy of pseudoephedrine in relieving congestion. A single dose of pseudoephedrine 60 mg was compared to placebo. Changes in nasal congestion were assessed through acoustic rhinometry and airway resistance was measured by posterior rhinomanometry. Nasal congestion and adverse effects were reported by participants through

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Oral Decongestants, Table 2 List of phenylephrine and pseudoephedrine products

Active Ingredient	Product name
Phenylephrine	Contact-D, Little Colds Decongestant, Nasal Decongestant PE Max Strength; Sudafed PE, Sudafed PE Maximum Strength, Sudogest PE
Pseudoephedrine	Decongestant 12 h Max St, Children's Silfedrine, ElixSure Congestion, Genaphed, Nexafed, Psudatabs, Simply Stuffy, Sudafed 12 h, Sudafed 24 h, Children's Sudafed, Sudafed, Sudanyl, SudoGest 12 h, SudoGest, Suphedrine, Unifed

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a five-point categorical score (Taverner et al. 1999). Fifty-two participants completed the study (25 were in the pseudoephedrine group and 27 were in the placebo group). The total nasal minimum cross-sectional area and nasal volume of the pseudoephedrine group increased significantly in comparison to placebo ($p = 0.018$ and $p = 0.003$, respectively). Nasal congestion was improved at all time points measured from 60 to 150 min after the dose.

Histamine receptor antagonists, such as cetirizine and loratadine, reduce symptoms of rhinorrhea, sneezing, and itching and are often combined with oral decongestants to help decrease nasal congestion. Studies combining the oral decongestant pseudoephedrine with loratadine, cetirizine, and desloratadine demonstrated that the combination therapy of oral decongestants with oral antihistamines was more effective in reducing symptoms of allergic rhinitis than if the individual components were administered alone (Bertrand et al. 1996; Bronsky et al. 1995; Grubbe et al. 2009).

While many studies support the efficacy of oral decongestants to relieve congestion symptoms associated with allergic/nonallergic rhinitis, adverse effects exist due to constriction of blood vessels throughout the body. Although these agents are considered safe, precautions should be taken in select patients. Oral decongestants should not be given to children who are below the recommended dosing range (see Table 1) due to the narrow therapeutic range between efficacy and toxicity. Oral decongestants are on the Beers Criteria for potentially inappropriate medications in older adults (Fick et al. 2003). A high severity rating is given for patients who have hypertension for concern for elevation of blood pressure due to vasoconstrictive properties of these agents (Fick et al. 2003). Additionally, renal function declines with increasing age. Therefore, the clearance of oral decongestants could increase in this patient population. The Beers Criteria also has a high severity rating for use of decongestants in patients with bladder outflow obstruction, such as benign prostate hyperplasia. Concern exists due to the fact that decongestants may decrease urinary flow and exacerbate urinary retention (Fick et al. 2003). Oral decongestants are not recommended in pregnancy, due to risks of vasoconstriction of the uterine arteries, thus decreasing fetal blood supply (Pray and Pray 2004). Oral decongestants also carry warning labels not to give oral decongestants to diabetics because these medications can increase blood glucose (Pray 2010). Oral decongestants have been implicated with the risk of stroke, and strong evidence with phenylproanolamine caused the FDA to ask manufacturers to halt the marketing of this product due to its risks (Cantu et al. 2003; Pray and Pray 2004).

Conclusion

Oral decongestants have been shown to reduce nasal congestion in patients with allergic/nonallergic rhinitis and sinusitis. Pseudoephedrine, now sold as a "behind the counter" medication, has limited availability because of recent illicit use in the synthesis of methamphetamine. State laws govern the availability of pseudoephedrine and may vary state to state. For example, in Oregon, pseudoephedrine is a class schedule III drug and requires a prescription. Oral decongestants also pose well-known safety concerns, and populations

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that should avoid these medications have been described. Additionally because of described adverse effects, caution should be exercised in long-term use.

Cross-References

► Intranasal Decongestants

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Oral Mast Cell Stabilizers

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Synonyms

Cromolyn; Ketotifen; Mast cell stabilizer

Definition

Oral mast cell stabilizers (OMCS) are administered for the treatment of allergic diseases including asthma and mastocytosis and have been used off-label for the treatment of food

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allergies. OMCS prevent the mast cell degranulation and release a host of active chemical mediators, including histamine and leukotrienes (LTs), inhibiting degranulation after contact with antigens. They are regarded as generally safe and associated with limited adverse effects.

Mechanism of Action

Mast cells have numerous biological functions which include a role in innate immunity, immune system immunomodulation, host defense mechanisms, and tissue repair. Mast cells are located in numerous tissues throughout the body and play an essential role in the prevalence of allergic diseases secondary to their hypersensitive response to otherwise innate substances that provoke an allergic reaction. They are activated by the interaction between the allergen and polyvalent IgE-FcεRI complexes found on the surface of mast cells as well as non-FcεRI complexes, which in turn leads to receptor aggregation. Various receptors and signaling proteins are then activated which leads to distinct signaling pathways, all part of a signaling cascade. Subsequent activation leads to the release of granule-associated mediators and lipid-derived mediators such as prostaglandins and leukotrienes and the synthesis of cytokines and chemokines which provoke instantaneous and chronic allergic inflammation (Metcalfe et al. 1997; Finn and Walsh 2013).

Mast cell stabilizers work by inhibiting the release of allergic mediators from mast cells and are mainly used clinically to prevent allergic reactions caused by common allergens. Two oral mast cell stabilizers exist: cromolyn and ketotifen. Cromolyn acts at the surface of mast cells to inhibit degranulation. This prevents the release of histamine and may reduce the release of inflammatory leukotrienes after contact with antigens. Ketotifen is a mast cell stabilizer and a relatively selective, noncompetitive H_1-antagonist and can also contract smooth muscle, alter the density and sensitivity of adrenergic receptors, decrease chemotaxis, and activate eosinophils. However, the exact mechanisms of action in relation to the therapeutic effects of oral mast cell stabilizers are not well understood (Gastrocrom 2006).

Clinical Trials

Oral mast cell stabilizers are used in the treatment and prevention of multiple different medical conditions. Oral cromolyn sodium is FDA indicated to treat systemic mastocytosis. Alternatively, it is used off-label to treat food allergies and gastrointestinal disorders such as irritable bowel disease and ulcerative colitis. Oral ketotifen is not approved in the United States, is labeled in Canada to treat atopic asthma, and is used off-label to treat atopic dermatitis, allergic rhinitis, chronic urticaria, and irritable bowel syndrome. Dosage formulations are shown in Table 1.

The use of cromolyn sodium has been studied in patients with mastocytosis in multiple clinical trials. A multicenter, double-blind, placebo-controlled trial evaluated cromolyn in 11 patients with systemic mastocytosis. Cromolyn was dosed at 200 mg four times daily compared to placebo while evaluating symptom severity score. Physician assessment of overall disease severity was improved with cromolyn compared to placebo at 4, 8, 12, and 16 weeks ($p < 0.02$, $p < 0.02$, $p < 0.03$, and $p < 0.05$, respectively). Patient daily symptom scores were also improved at 8 and 16 weeks ($p < 0.028$ for both) (Horan et al. 1990). A double-blind, active-controlled, crossover study evaluated the use of cromolyn 200 mg four times daily compared to the combination of chlorpheniramine 4 mg four times daily and cimetidine 300 mg four times daily in eight patients with mastocytosis. Both treatment arms showed symptom improvement in regard to patient symptom scores and physician evaluations. No statistically significant difference was observed between the two treatment arms (Frieri et al. 1985).

Case reports have demonstrated the effectiveness of cromolyn in patients with food allergies (Juji and Suko 1994). A case report of two children reported oral cromolyn to prevent

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Oral Mast Cell Stabilizers, Table 1 Oral mast cell stabilizer availability, dosage forms, and dosing information (Gastrocrom® package insert 2006)

Generic name	Cromolyn (Gastrocrom package insert, 2002)	Ketotifen
Brand name	Gastrocrom®	Apo-Ketotifen®, Novo-Ketotifen®, Zaditen®
Availability/ regulatory status	The United States and Canada/Rx and OTC	Canada and Europe
Dosage form	Oral solution	Capsule, tablet, oral suspension
Adult indication/ dosage	**Treatment of systemic mastocytosis** 200 mg orally four times daily, 30 min before meals and at bedtime. The maximum recommended dose is 40 mg/kg/day	**Allergic rhinitis, atopic dermatitis, acute or chronic urticaria** 1 mg orally every 12 h, sustained release can be taken once daily
	Prevention of symptoms associated with food allergy (unlabeled use) 200 mg orally four times daily, given 15–20 min before meals. The same dosage has been used as maintenance therapy to prevent relapse For patients requiring occasional therapy, 200 mg orally 15–20 min prior to the precipitating meal may be used; however, the optimal dose should be individualized	
Pediatric indication/ dosage	**Treatment of systemic mastocytosis** Children 2–12 years: 100 mg orally four times per day, 30 min before meals and at bedtime. Dosage should not exceed 40 mg/kg/day orally Children and infants 6–23 months: Initially, 20 mg/kg/day orally given in 4 divided doses. May be increased if benefits are not observed after 2–3 weeks up to 30 mg/kg/day orally Infants <6 months: Dosage should not exceed 20 mg/kg/day orally, administered in four divided doses	**Allergic rhinitis, atopic dermatitis, acute or chronic urticaria** 0.5 mg orally every 12 h
	For the prevention of symptoms associated with food allergy (unlabeled use) Children and adolescents 2–14 years: Initially, 100 mg orally four times per day given 15–20 min before meals. The same dosage has been used as maintenance therapy to prevent relapse For patients requiring occasional therapy, 100 mg orally 15–20 min prior to the precipitating meal may be used; however, the optimal dose should be individualized	

food-dependent exercise-induced anaphylaxis (FDEIA), when it was taken before the intake of the causative food (Sugimura et al. 2009). Another case report investigated the use of oral cromolyn to prevent the symptoms of FDEIA in a patient and allowed him to eat a nonrestricted diet and continue a high level of physical training (Benhamou et al. 2007). Cromolyn has also been used effectively to decrease adverse effects in patients undergoing oral-specific desensitization with foods (Patriarca et al. 2007). A case study demonstrated successful treatment with oral cromolyn in a child with a severe anaphylaxis to ingestion of milk and milk-containing foods. The patient was able to eventually tolerate small amounts of milk and even moderate amount of food containing milk after 3 months of oral cromolyn therapy (Jones 1985).

Ketotifen is not currently available in the United States, but evidence suggests utility in

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allergy diseases. Ketotifen acts as a dual-action agent: antihistamine and mast cell stabilizer. A double-blind, placebo-controlled randomized study evaluated the use of ketotifen 1 mg twice daily compared to cetirizine 10 mg daily, oxatomide 1 mg/kg, and placebo in 69 children aged 6–12 with perennial allergic rhinitis. Ketotifen improved total symptom scores at weeks 4, 8, and 12 ($p < 0.01$) and improved symptoms of sneezing and itchy eye scores at weeks 8 and 12. No statistical significant findings were observed for nasal symptoms, tickly throat, watery eyes, nocturnal cough, or nasal expiratory flow rate compared to placebo. Ketotifen was well tolerated. In comparison, cetirizine showed the largest decrease in overall symptoms and was significantly more effective at reducing the mean rhinorrhea score compared to oxatomide ($p < 0.01$) and ketotifen ($p < 0.01$) (Lai et al. 2002).

Ketotifen has also exhibited efficacy in treating urticaria. A small prospective study observed four patients with cholinergic urticaria with cardiorespiratory manifestation. All four patients had proven to be refractory to conventional antihistamine therapy. Doses of ketotifen ranging from 3 to 8 mg daily resulted in clinical improvement, confirmed through a repeat exercise challenge. Three of the four subjects demonstrated blockade of mast cell mediator release, while the remaining subject demonstrated a rise in histamine levels to half of the peak observed prior to being treated with ketotifen. Based on plasma histamine concentrations and comparisons with and without ketotifen therapy, the study observed ketotifen as both an H_1 histamine-receptor antagonist and mast cell stabilizer (McClean et al. 1989).

Safety and Side Effects

Adverse effects caused by oral administration of mast cell stabilizers are usually mild and transient. The most frequent adverse effects of cromolyn from clinical studies included headache and diarrhea (Frieri et al. 1985; Horan et al. 1990). The most common side effect of ketotifen observed in clinical studies was sedation (Lai et al. 2002). Less common side effects include dizziness, nausea, headache, dry mouth, and weight gain (Grant et al. 1990).

Drug Interactions

There are no known major drug interactions with Gastrocrom.

Ketotifen has been associated with the potentiation of central nervous system depressant effects when used concomitantly with sedatives, hypnotics, antihistamines or alcohol (Zaditen product information 2010).

Conclusion

Oral mast cell stabilizers are not typically used first line for allergic conditions. However, due to the effect of mast cells on the development and maintenance of certain allergic diseases, they can be considered as an alternative therapy. Cromolyn sodium is approved for use in patient's mastocytosis. There is some evidence for the use of cromolyn in treating food-dependent, exercise-induced anaphylaxis. Although oral ketotifen is not approved for use in the United States, there is limited evidence showing its benefits over placebo in allergic rhinitis. Oral mast cell stabilizers can be used as a safe alternative therapy in the treatment of allergic diseases, other than mastocytosis, which provide benefit to select patient populations due to their minimal side effect profiles.

Cross-References

- ▶ Activating and Inhibitory Receptors on Mast Cells
- ▶ Intranasal Mast Cell Stabilizers
- ▶ Mast Cell Mediators
- ▶ Mast Cells, Growth and Development
- ▶ Morphology and Histologic Identification of Mast Cells

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Pathophysiology of Anaphylaxis

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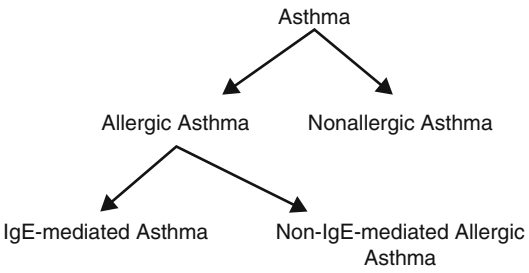
Synonyms

Anaphylactic reaction; Anaphylactic shock; Anaphylactoid reaction; Life-threatening allergy

Definition

The historic nomenclature for anaphylaxis reserved the term "anaphylactic" for reactions mediated by immunoglobulin E (IgE) and the term "anaphylactoid" for reactions that were not IgE-mediated (Sampson et al. 2006). IgE-mediated and non-IgE-mediated reactions are, however, typically clinically indistinguishable. It is therefore now considered preferable to use the term "anaphylaxis," irrespective of the mechanism involved. These reactions can then, if necessary, be subclassified as "immunologic" (i.e., IgE-mediated and non-IgE-mediated [e.g., IgG- and immune complex complement-mediated]) and "non-immunologic" (i.e., events resulting in sudden mast cell and basophil degranulation in the absence of immunoglobulins) reactions, as shown in Fig. 1 (Johansson et al. 2004).

Anaphylaxis is a multisystem reaction that results from the sudden release of histamine and a variety of other inflammatory mediators, including interleukins (IL-3, IL-4), STAT-6, chymases, proteases, tryptases, prostaglandin D2, leukotriene B4, platelet-activating factor (PAF), and cysteinyl leukotrienes (LTC4, LTD4, and LTF4) from mast cells and basophils. This then results in smooth muscle spasm, vasodilatation, increased vascular permeability, increased mucus secretion, increased muscle tone, and edema (Greenberger and Ditto 2012).



Pathophysiology of Anaphylaxis, Fig. 1 Classifying allergic reactions using the example of asthma (Reprinted with permission from Johansson et al. 2004)

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Cross-References

- Anaphylaxis, Background
- Anaphylaxis, Clinical Manifestations and Diagnosis
- Biphasic, Protracted, and Late-Phase Reactions in Anaphylaxis
- Etiology of Anaphylaxis
- Management of Anaphylaxis
- Mast Cell Mediators Associated with Anaphylaxis

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Peanut Allergy

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Definition

Peanuts represent as one of the most important foods involved in the development of food allergy. The incidence and prevalence of peanut allergic individuals, particularly in childhood, is steadily growing. Regional differences have been observed. Particularly in North America and England, peanut allergy is a heavily growing problem.

Symptoms range from intestinal and abdominal presentations, including diarrhea, vomiting, and pain, and skin reactions (urticaria) to the airways and the lung (bronchial asthma). The most severe reaction is anaphylaxis and anaphylactic shock which is a life-threatening emergency, requiring immediate attention and treatment with adrenalin. The most common route of exposure is peanut ingestion. However, it might be possible that sensitization occurs also through external exposure, particularly in patients suffering from atopic dermatitis, having a disrupted skin barrier. The importance of external exposure for primary sensitization is controversial, although in sensitized patients topical exposure causes typical immediate hypersensitivity responses with rush exacerbation of eczema and urticarial lesion.

As with any other food allergies, the underlying pathomechanism is the development of immediate-type hypersensitivity response (type I reaction). This response is mainly based on the development of IgE antibodies, specifically reacting with the allergens. The development of these antibodies is dependent on the formation of allergen-specific TH2 T-cells, producing IL-4, IL-5, IL-9, and IL-13 among other cytokines. The effector response includes involvement of mast cells and eosinophils, which are also controlled by TH2 T-cells.

The diagnosis is based on the same pillars as any other food allergies. Taking a detailed history, testing for peanut-specific IgE antibodies, and the food challenge preferable under double-blind placebo-controlled condition represent the most important cornerstones.

Treatment consists of avoidance of peanuts and peanut-containing products. New avenues using specific forms of immunotherapy (oral or injected peanut desensitization) are currently under development and clinical evaluation.

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Cross-References

- Allergen Avoidance: Dietary Management of Food Allergy
- Diagnostic Food Challenges
- Egg Allergy
- Fatal Allergic Reactions to Foods
- Food Allergens
- Food Allergies, Diagnostic Testing
- Food Allergy and its Future Treatment
- Food Allergy, Overview
- Food Desensitization
- Methods (In Vivo) Provocation Tests (Nasal Challenge, Bronchial Challenge, Food Challenge)
- Peanut Allergy
- Urticaria

Peanut Allergy, Diagnosis and Management

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Synonyms

Peanut hypersensitivity; Peanut sensitization

Definition

Peanut allergy is an IgE-mediated hypersensitivity reaction to peanut, a member of the legume family of plants.

Epidemiology

The prevalence of peanut allergy is dependent upon multiple factors including age, geographic location, and race and/or ethnicity. While determining accurate rates of peanut allergy is challenging due to inconsistent diagnostic criteria and variable clinical presentation, worldwide prevalence is estimated to be around 1 %. Prevalence rates in children are higher than in adults, ranging from 0.2 % in Israel to 1.9 % in the United Kingdom. In the United States, the self-reported prevalence of peanut allergy as of 2010 was 1.3 % overall, with 1.4 % of children and 0.6 % of adults reporting clinical reactivity. In general, reported rates of peanut allergy are less in Asia than in North America, Europe, or Australia. Furthermore, rates of peanut sensitization are significantly higher than those for clinical reactivity in most populations (Sicherer 2011).

It is generally thought that the prevalence of peanut allergy in Western countries has increased over the past few decades. In the United States, self-reported peanut allergy among children increased from 0.4 % to 1.4 % between 1998 and 2010. Rates among adults were stable at 0.6–0.7 % during the same period (Sicherer et al. 2010a). A sequential cohort study over a period of 7 years demonstrated increased sensitization to peanut from 1.1 % to 3.3 % among children ages 3–4 years (Grundy et al. 2002). Several theories have been proposed for the apparent increasing hypersensitivity to peanuts, including increased peanut consumption, environmental exposure to peanut allergens through non-enteral routes, and regional variations in preparation of peanut products (e.g., roasting peanuts in Western societies) (Boulay et al. 2008).

The development of peanut allergy is likely due to a complex combination of genetic and environmental factors. The concurrence of peanut allergy among monozygotic twins is 64 %. Moreover, having a sibling or parent with peanut allergy increases a patient's risk of developing peanut allergy by sevenfold (Lack 2008). The development of peanut allergy as a result of peanut exposure during pregnancy and/or lactation remains an area of debate. Maternal consumption of peanuts during pregnancy was associated with increased peanut sensitization in infants 3–15 months of age, although clinical reactivity to peanuts was not assessed

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(Sicherer et al. 2010b). Interestingly, observational studies have noted a relatively low prevalence of peanut allergy in societies where peanuts are consumed in high quantities during pregnancy and early childhood, such as in Asia and Africa (Lack 2008). Given a lack of conclusive evidence, current guidelines sponsored by the National Institute of Allergy and Infectious Disease do not recommend restricting maternal diet during pregnancy or lactation as a means to prevent food allergy (Boyce et al. 2010). The timing of introduction of peanuts to infants has also been recently revised. Prior recommendations to delay introduction of peanut until age 3 years have been withdrawn due to insufficient evidence that this practice affected the development of food allergies (Greer et al. 2008). Further high-quality studies are necessary to clarify the role of maternal and infant dietary practices in the development of peanut allergy.

Most patients with peanut allergy have concurrent atopic disease, including other food allergies, atopic dermatitis (eczema), allergic rhinitis, and asthma. Nearly three-fourths of peanut-allergic children demonstrate sensitization to one or more other foods, with egg, milk, and tree nuts being most common (Green et al. 2007). One-third of patients with peanut allergy can be expected to react to tree nuts. Reactivity to most other legumes, such as soybeans and green peas, is unusual (less than 5 %) save for lupine, which appears to have a cross-reactivity of about 30 % in peanut-allergic patients (Boyce et al. 2010). About 30–40 % of patients with moderate to severe atopic dermatitis have a clinically significant IgE-mediated food allergy, with peanut being a common allergen. In addition, atopic dermatitis during early infancy appears to increase the risk of developing peanut allergy later in life (Lack 2008).

Pathogenesis

The pathogenesis of peanut allergy, like other food allergies, is presumed to involve a skewing toward Th2-like immune responses and loss of immunoregulatory mechanisms. During the initial sensitization phase, ingested peanut proteins, which are heavily glycosylated and resistant to digestion, are taken up in the intestines by specialized epithelial cells (M cells) or by dendritic cells that can directly sample antigen from the gut lumen. The proteins are then processed and presented to naïve peanut-specific CD4+ T cells, which differentiate into Th2 cells secreting IL-4, IL-5, and IL-13. These cytokines induce peanut-specific B cells to undergo antibody class switching and produce IgE, which then binds to high affinity surface IgE receptors on mast cells and basophils. When peanuts are subsequently ingested, absorbed peanut protein binds to and cross-links the specific IgE on mast cells and basophils, resulting in cell activation and release of several vasoactive and inflammatory mediators such as histamine, prostaglandins, and platelet-activating factor. These molecules elicit local symptoms in the gastrointestinal tract, including nausea, vomiting, diarrhea, and abdominal pain, or may act systemically causing urticaria, angioedema, bronchospasm, hypotension, and arrhythmias (Sampson and Burks 2009).

At least nine peanut allergens (Ara h 1–9) have been identified. Ara h 1–2 are the immunodominant antigens, with nearly 95 % of peanut-allergic patients in the United States sensitized to these allergens. Ara h 3 is also a notable allergen with sensitization rates of 45 %, while the remaining proteins bind to IgE in a much smaller percentage of peanut-allergic patients. Most peanut allergens, with the exception of Ara h 5, 8, and 9, are homologous to seed storage proteins. These proteins are generally resistant to chemical and proteolytic degradation – characteristics that likely contribute to their allergenicity by preventing complete digestion and allowing absorption of relatively intact peanut protein from the gut lumen (Scurlock and Burks 2004). Ara h 5, 8, and 9 are thought to be associated with oral allergy syndrome (OAS) in sensitized patients. Ara h 5 is a profilin, which is a family of plant structural proteins involved with cytoskeleton formation. Ara h 8, a member of the pathogen-related 10 family of plant proteins, shares homology with the birch pollen

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allergen Bet v 1. Ara h 9, is a nonspecific lipid transfer protein recognized by some Mediterranean patients with sensitization to peach allergens (Krause et al. 2009).

Clinical Features

Allergic reactions to peanuts are primarily IgE-mediated and are characterized by the rapid onset of symptoms involving the skin (urticaria, angioedema, pruritus), gastrointestinal tract (oral pruritus, vomiting, diarrhea, abdominal cramping), and/or respiratory tract (persistent coughing, dyspnea, bronchospasm, laryngoedema). Objective symptoms occur within seconds to 2 h after ingestion of peanuts, with a median time of onset of 3 min. Reactions typically occur with ingestion of 1–3 peanut kernels (>162 mg of peanut protein), although extremely sensitive patients may react to as little as 5 mg of peanut protein (Sicherer 2002). The median age of the initial clinical reaction is 14 months, which appears to have decreased over the past decade (Green et al. 2007). For the majority of patients, the original clinical reaction happened with the first known ingestion of peanuts, indicating that sensitization likely occurs through occult exposures. Nearly 90 % of patients experience cutaneous symptoms during their initial clinical reaction. Respiratory and gastrointestinal symptoms are present in one-half and one-third of allergic patients, respectively, although these rarely occur as the sole manifestation of peanut hypersensitivity (Sicherer et al. 1998).

Peanuts are a leading cause of food-induced anaphylaxis, a severe and potentially fatal systemic allergic reaction that can present with any combination of the above IgE-mediated symptoms along with cardiovascular events including hypotension, syncope, and cardiac dysrhythmias. Biphasic reactions, characterized by recurrent symptoms 4–6 h after the initial event, occur in about one-third of patients with fatal or near-fatal anaphylaxis. The likelihood of anaphylaxis in allergic patients following peanut ingestion is variable and may occur in the absence of a history of prior severe reactions. Patients with poorly controlled asthma or a prior history of anaphylaxis are at increased risk of severe food-induced anaphylaxis. Adolescents and young adults with peanut allergy are also at increased risk for fatal or near-fatal reactions due to risk-taking behaviors. Neither the level of specific IgE in the serum nor the skin prick wheal size accurately predicts the severity of allergic reactions to peanut (Boyce et al. 2010).

Other clinical reactions to peanuts that are at least partially dependent upon IgE are OAS and atopic dermatitis. OAS occurs in patients with sensitization to plant pollen allergens, such as birch pollen, which share homology to certain peanut allergens. Symptoms, which occur after the ingestion of various raw fruits and vegetables, are typically localized to the oropharynx and include pruritus, angioedema of the lips or palate, and occasional throat tightness. Peanut ingestion may exacerbate atopic dermatitis in sensitized patients through both IgE- and non-IgE-mediated mechanisms. Finally, immune reactivity to peanuts has been implicated in non-IgE-mediated food allergies, such as eosinophilic esophagitis, although further studies are needed to delineate the exact pathogenic mechanisms of these disorders (Sampson and Burks 2009).

Diagnosis

An accurate diagnosis of peanut allergy is dependent upon a compelling history of immediate clinical reactivity following the isolated ingestion of peanut in combination with evidence of peanut-specific IgE (i.e., sensitization). When interviewing a patient with suspected peanut allergy, it is important to determine the temporal association between eating peanuts and the onset of symptoms, the type of symptoms experienced, the amount of peanut protein ingested, the symptoms after eating similar foods, and whether other potentially allergenic foods were ingested. As noted above, IgE-mediated peanut allergy typically presents with some combination of cutaneous, gastrointestinal, or respiratory symptoms within minutes of consuming peanuts.

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Although the symptoms and severity of reactions may vary, patients should experience some degree of clinical reactivity with every episode of peanut ingestion. The differential diagnosis for peanut allergy includes hypersensitivity to other food allergens (tree nuts, sesame seeds), idiopathic urticaria and anaphylaxis, and mastocytosis. Psychological reactions including panic disorders and food phobias should also be considered (Sampson and Burks 2009).

Peanut-specific IgE can be detected by a skin prick test (SPT) or in vitro IgE testing. These tests should not be used for general screening purposes, as up to 9 % of the United States population have detectable peanut-specific IgE, yet only 1–2 % have clinical reactivity. However, there are certain clinical scenarios where testing for peanut-specific IgE in the absence of a clinical history may be considered, such as having a sibling with peanut allergy (Boyce et al. 2010).

SPTs are safe and convenient tests that can yield rapid results typically within 20–30 min. A SPT with a wheal mean diameter >3 mm than the negative control is considered positive. It is important to note that a positive SPT alone has a poor predictive value and therefore is not diagnostic. Wheal size, though, can be helpful in predicting the likelihood of peanut hypersensitivity but not the severity of reaction. In children suspected of having peanut allergy, a wheal size >8 mm was associated with a greater than 95 % chance of clinical reactivity following peanut ingestion (Roberts and Lack 2005). A negative SPT has a good negative predictive value and therefore is helpful at ruling out peanut allergy. However, a negative SPT in the setting of a highly suspicious clinical history of peanut reactivity should be interpreted cautiously.

Peanut-specific serum IgE testing is also helpful for assessing sensitization, although, like the SPT, it alone is not diagnostic. Studies using the ImmunoCAP system (Phadia, Uppsala, Sweden) have shown that a peanut-specific IgE of 14 kU/L or greater has a positive predictive value of 95 % in patients with suspected peanut allergy (Maloney et al. 2008). On the other hand, an undetectable peanut-specific IgE test does not completely rule-out peanut allergy, especially in a patient with a convincing history. The level of peanut-specific IgE also does not correlate with the magnitude of the allergic reaction, and therefore, a patient with a level of >100 kU/L is not necessarily considered to have a more "severe" peanut allergy than a patient with a level of 15 kU/L.

A patient with an unequivocal history of symptoms consistent with an IgE-mediated reaction following a known peanut ingestion and evidence of peanut-specific IgE does not typically require further diagnostic studies. If the history is ambiguous or peanut-specific IgE is not evident, then a physician-supervised food challenge should be performed. The double-blind placebo-controlled food challenge (DBPCFC) is considered the gold standard for the diagnosis of IgE-mediated food allergies but is expensive and burdensome and therefore seldom used in clinical practice. An open or single-blinded food challenge can be an acceptable alternative to DBFCFC. If no symptoms are elicited during a graded open food challenge, then peanut allergy can be effectively ruled out. Given their inherent risk, an oral food challenge should be performed by trained health-care providers in a medical facility that is equipped to treat potential anaphylaxis (Boyce et al. 2010).

Intradermal skin testing for peanut allergy has no clear benefit over SPT and is associated with greater risk of systemic reactions and, therefore, is not recommended for diagnosis. Other experimental or nonstandardized tests that should not be used for diagnosing peanut allergy include basophil histamine release/activation tests, patch testing, allergen-specific IgG and IgG4, and in vitro lymphocyte stimulation assays (Boyce et al. 2010).

Management

Strict dietary avoidance of peanuts remains the cornerstone for managing peanut allergy. Patients and their families should be educated on how to read food labels and identify products that contain peanuts. The Food Allergen Labeling and Consumer Protection Act (FALCPA)

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requires that all food products sold in the United States must clearly state if peanuts or other major allergens are present. The European Union has also enacted similar legislation. Advisory labels indicating that a product "may contain peanuts" are not regulated, and thus, it is generally recommended that patients avoid such labeled foods. Highly refined peanut oils do not contain appreciable amounts of protein and therefore are safe to consume; however, cold-pressed peanut oils may contain peanut protein and are potentially hazardous. Patients should abstain from eating unlabeled candies or desserts and should be aware of high-risk dining venues where peanut cross-contamination is likely, such as buffets, bakeries, ice cream parlors, and Asian or Mexican ethnic restaurants. Despite strict avoidance measures, accidental exposures will invariably occur with an annual incidence rate of about 14 % (Burks 2008).

Peanut-allergic patients are typically advised to avoid tree nuts, as cross-reactivity is present in about one-third of patients. For older patients who are intent upon adding tree nuts to their diet, it is prudent to first screen them for tree nut-specific IgE either by SPT or in vitro assays. If negative, they should be advised to eat only tree nuts that are clearly identifiable. Despite high cross-reactivity rates of peanut-specific IgE with other legumes (soy, peas, string beans), clinical reactivity is rare and it is generally safe for peanut-allergic patients to consume other legumes. One exception is lupine, which appears to have higher rates of clinical cross-reactivity and should therefore be avoided (Boyce et al. 2010). Overall, the risks and benefits of avoiding other potential allergens are unique for each patient and will depend upon the patient's preferences and their prior clinical reactions.

All patients with peanut allergy should be prescribed an epinephrine autoinjector and should be thoroughly instructed on its proper use and indications for administration. The patient should be provided with a written food allergy action plan that clearly indicates the appropriate dosing of self-injectable epinephrine and antihistamines (e.g., diphenhydramine, cetirizine). Schools, child-care facilities, and camps should also be provided with a copy of the food allergy action plan and have protocols in place for managing acute reactions. Reactions comprised of localized cutaneous findings or mild upper respiratory symptoms (i.e., nasal congestion) can typically be treated with antihistamines alone and close observation. Patients with more generalized cutaneous reactions, significant gastrointestinal symptoms, or lower respiratory tract symptoms should be given self-injectable epinephrine. In addition, the emergency response system should be activated in the event that further life-saving interventions are needed. Patients with generalized reactions should be monitored in a medical facility for at least 4 h due to the possibility of a biphasic reaction (Sampson and Burks 2009).

Patients with food-induced anaphylaxis should be treated aggressively with intramuscular epinephrine, supplemental oxygen, and volume resuscitation with intravenous fluids (Boyce et al. 2010). Histamine H1- and H2-receptor antagonists, bronchodilators, and glucocorticoids are also frequently administered, but it is important to remember that these therapies are not a substitute for epinephrine and will not reverse laryngeal edema or cardiovascular collapse. While efficacy data is lacking, most patients receive a 3-day course of oral glucocorticoids and antihistamines for the prevention of biphasic reactions.

Patients with peanut allergy should be evaluated every 1–2 years to inquire about accidental exposures, reassess peanut sensitization, and reinforce education regarding allergy management. While once thought to be a lifelong diagnosis, it is now believed that about 20 % of children will outgrow their peanut allergy. Predictors of peanut allergy resolution are variable, but generally a decreasing level of peanut-specific IgE during the first 5 years of life is a good prognostic sign. Patients who have not had reactions in the past 12–24 months and have low or undetectable levels of peanut-specific IgE (wheal diameter <8 mm and serum IgE <2 kU/L) should be considered for an oral food challenge (OFC) to confirm resolution of peanut hypersensitivity. Due to safety concerns, OFC is typically only offered to patients 4 years of age or

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older, although this is not a strict requirement. If a patient has a negative food challenge, they should be encouraged to consume peanuts regularly (at least weekly), as those who consume peanuts intermittently or not at all have higher rates of peanut allergy recurrence (Byrne et al. 2010).

Several novel therapies for peanut allergy are under investigation, including oral immunotherapy (OIT), sublingual immunotherapy (SLIT), vaccination with modified peanut allergens and immunomodulatory agents, and treatment with anti-IgE monoclonal antibodies. OIT and SLIT trials have demonstrated desensitization to peanut in allergic patients, although durable induction of tolerance remains to be determined. While preliminary findings are encouraging, these novel therapeutic methods are not ready for use in the clinical setting until long-term efficacy and safety are established (Nowak-Wegrzyn and Sampson 2010).

Conclusion

Peanut allergy affects about 1 % of the population and appears to be increasing in prevalence. Diagnosis is dependent upon a clinical history consistent with an immediate hypersensitivity reaction following the ingestion of peanut and evidence of specific IgE. Skin prick testing and in vitro peanut-specific IgE assays are helpful tools in the evaluation of a patient with possible peanut allergy, but alone are not diagnostic and do not predict clinical severity. Oral food challenges should be reserved for patients with an equivocal clinical history or for verifying allergy resolution. Strict dietary avoidance of peanut remains the cornerstone of management. Patients and their families should receive routine education regarding early recognition of allergic symptoms and strategies for allergen avoidance. Because peanut allergy is potentially life threatening, all patients should be given an emergency action plan and be prescribed self-injectable epinephrine. Mild reactions can typically be managed with antihistamines and close monitoring, whereas more severe reactions involving the respiratory tract or cardiovascular system require prompt treatment with epinephrine and immediate medical evaluation. Novel therapies such as peanut-specific OIT and SLIT are promising but remain investigational at this time. Since peanut allergy is outgrown in approximately 20 % of patients, routine follow-up by an allergist is recommended.

Cross-References

- ▶ Diagnostic Food Challenges
- ▶ Fatal Allergic Reactions to Foods
- ▶ Food Allergens
- ▶ Food Allergies, Diagnostic Testing
- ▶ Food Allergy and its Future Treatment
- ▶ Food Allergy, Overview
- ▶ Food Desensitization

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Photoallergic Contact Dermatitis

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Synonyms

Allergic photodermatitis

Definition

A type IV hypersensitivity reaction against a substance, which has become an allergen through chemical modification by irradiation with ultraviolet or visible light. It manifests as a papulovesicular or exudative dermatitis occurring primarily on the light-exposed areas of the skin. The gold standard for diagnosing photoallergic contact dermatitis (PACD) is the photopatch test.

Occurrence

PACD shows random occurrence, mostly adults are involved. The most frequent triggers are sunscreens, cosmetics, and nonsteroidal anti-inflammatory drugs (NSAIDs) (Goossens 2004; Kerr and Ferguson 2010).

Historical Background

Half a century ago, Wilkinson (1962) first described a relationship between the incidence of PACD and the use of halogenated salicylanilides (tetrachlorosalicylanilide) in deodorant soaps as antibacterial agents. This observation was due to the epidemic development of PACD in workers of industrial enterprises producing deodorant soaps who used the soaps by themselves. In the following years, antimicrobial agents, antimycotics, and preservatives have been identified as potential photoallergens (Ippen 1961; Coxon et al. 1965; Freeman and Knox 1968; Burry 1967, 1970). Until now, photoallergy has been reported against almost all organic chemical agents that absorb UV radiation.

Since the 1990s, sunscreens have become the most common cause of PACD, due to their widespread use (Fitzpatrick 1999; Goossens 2004) and the multiple components of potential photosensitizers. Among those, benzophenone is a common cause of photoallergy (De Leo et al. 1992; Szczurko et al. 1994).

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Elicitors of PACD

Sunscreen Ingredients

A wide array of sunscreen ingredients, often included as preservatives, can elicit a PACD (i.e., para-aminobenzoic acid (pabanol), benzophenones, 4-methylbenzylidene camphor, isopropyl dibenzoylmethane, butyl methoxydibenzoylmethane, 2-ethylhexyl-4-(dimethylamino) benzoate, 2-ethylhexyl-p-methoxycinnamate, phenylbenzimidazole sulfonic acid, isoamyl-p-methoxycinnamate).

Nonsteroidal Anti-inflammatory Drugs (NSAIDs)

NSAIDs have been increasingly used in the treatment of musculoskeletal pain. Among them, ketoprofen has a well-known high potential as photoallergen (Oiso and Kawada 2011). PACD has also been attributed to other NSAIDs such as ibuprofen, suprofen, tiaprofenic acid, diclofenac, etofenamate, piroxicam, indometacin, and benzydamine.

Fragrances

Besides sunscreen ingredients and NSAIDs, fragrances are also frequent elicitors of photoallergic reactions. In the 1970s and 1980s, musk ambrette, used in men's aftershaves, was a common photosensitizer, and even cases of persistent photosensitivity have been reported, following initial photoallergic reactions (Burry 1981; Cronin 1984; Ramsay 1984). Other examples are methylcoumarin, used in suntanning lotions and perfume mixtures.

Antibacterials

Antibacterials form another common group of photosensitizers. Among those, halogenated salicylanilides are well-known photoallergens (Wilkinson 1962; Coxon et al. 1965; Freeman and Knox 1968), such as tetrachlorosalicylanilide, tribromosalicylanilide, hexachlorophene, bithionol, and sulfanilamide. Antimycotics are also potential photoallergens, namely, fenticlor, multifungin (Burry 1967), and a-chlor-2-hydroxybenzoesaure-N-n-butylamid (Jadit) (Ippen 1961).

Others

Agricultural pesticides, herbal ingredients, etc.

Pathophysiology

The action spectrum of the light which is able to induce a photoallergen mainly lies in the UVA range, only in few cases UVB light is also involved (NSAIDs, for example, can become photoallergens by both UVA and UVB irradiation) (Goossens 2004). Radiant energy converts a substance taken up into the skin into a photoactive compound, thereby becoming an immunogenic allergen, which initiates an immune cell-mediated type IV hypersensitivity reaction. This may happen via the production of stable haptens, which after conjugation with a carrier protein can be taken up by antigen-presenting cells like epidermal Langerhans or dermal dendritic cells and processed for presentation to and activation of T cells in the regional lymph nodes (sensitization phase). Alternatively, the photoallergen may be first converted by radiant energy to a higher unstable energy state, and, on returning to resting state, the released energy promotes conjugation of the molecule to a carrier protein, forming a complete new antigen (Stein and Scheinfeld 2007).

Allergen-specific T cells will migrate to the skin and become reactivated when the skin is exposed to the photoallergen again, which results in the induction of an inflammatory response (elicitation phase) (Fitzpatrick 1999; Mang and Krutman 2001). Rarely, patients continue to develop skin lesions despite strict avoidance of the culprit photoallergen. This clinical entity is called chronic actinic dermatitis. Cutaneous persistence of the photoallergen or the formation of an endogenous photosensitizer is discussed as possible reason for this phenomenon (White 2001).

Clinic

Eczematous lesions are found in a symmetrical distribution on light-exposed skin like the face, neck, upper chest, forearms, and dorsum of the

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Photoallergic Contact Dermatitis, Fig. 1 Photoallergic dermatitis induced by repeated topical use of a sunscreen agent containing methoxycinnamate, butyl methoxydibenzoylmethane, and phenylbenzimidazole sulfonic acid

Photoallergic Contact Dermatitis, Fig. 2 Photoallergic dermatitis induced by repeated topical use of a sunscreen agent containing methoxycinnamate, butyl methoxydibenzoylmethane, and phenylbenzimidazole sulfonic acid

hands or legs (Figs. 1 and 2). Regions of the head naturally not receiving sunlight (i.e., eyelids, behind the ears, and below the chin) are typically not affected. Sometimes, patients present with circumscribed lesions or an asymmetrical distribution, which may be due to unilateral application of the photoallergen or enhanced sun exposure of this body site.

Diagnostic

Laboratory tests are of no use. The most effective and widely used method to diagnose photoallergic contact dermatitis is the photopatch test. However, standardized methods concerning irradiation wavelength, UV dosage, duration of application of the agent, and postirradiation time points for the evaluation still need to be established between different centers and countries (Kerr and Ferguson 2010).

Usually, the potential photoallergens are solved in a vehicle (mostly petrolatum) and are then placed within hypoallergenic plastic or metal chambers on the patient's back. After a variable period of time (between 13 and 48 h), the allergens are removed and the skin is usually irradiated with UVA (dose range between 5 and 10 J/cm^2). At different time points after irradiation (between 0 and 168 h, usually multiples of 24 h), test sides are monitored for a positive reaction. To rule out a false-positive result due to a non-photoallergic contact dermatitis elicited directly by the tested component, allergens are applied in duplicates but only one test side is irradiated.

Differential Diagnosis

Systemic Photoallergic Dermatitis

The clinical findings are often indistinguishable from photoallergic contact dermatitis, except that

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the allergen is not introduced percutaneously but enterally or parenterally. Major systemic photoallergens are antimicrobials (i.e., sulfonamides, lomefloxacin, chloramphenicol), antihypertensive agents (hydrochlorthiazide, chlortalidone, quinethazone), phenothiazines, NSAIDs (piroxicam, celecoxib), and antimalarials (chloroquine, hydroxychloroquine, quinidine) (Stein and Scheinfeld 2007). Widespread eruptions may suggest systemic photosensitizers, while topical photosensitizers mainly produce lesions in areas that have been exposed to both sensitizers and radiation.

Phototoxic Dermatitis

An inflammatory skin reaction induced in UV-light-exposed skin areas, not due to an allergen-specific immune reaction but rather the result of toxic skin damage. It manifests as acute dermatitis with redness, edema, vesicles, or blister formation, within hours and strictly circumscribed to the irradiated skin. The most common form is a trivial sunburn; however, it can also be induced by phototoxic agents such as fragrances (i.e., bergamot oil), dyes (i.e., acridines, eosin), or different drugs (i.e., diuretics, antibiotics, antipsychotics, NSAIDs).

Polymorphic Light Eruption: A polymorphous skin disease, due to the action of sunlight. The skin eruptions develop in the spring, usually with the first intensive sun exposure, and then disappear during the summer (hardening effect) to reappear almost routinely in the following year. Only skin-exposed areas are affected by symmetrically distributed non-scarring erythematous papules, vesicles, wheals, or plaques.

Chronic Actinic Dermatitis (*CAD*): Chronic eczematoid photodermatosis in light-exposed areas, characterized by persisting photosensitivity without exposure to an external photosensitizer. It is induced and maintained by exposure to often very small amounts of UVB and UVA, and sometimes also visible radiation. It is considered to be an acquired, delayed-type hypersensitivity reaction to endogenous, photoinduced antigens. CAD usually affects the middle-aged or elderly, approximately 90 % of patients being male. CAD is the general heading for different light dermatoses, such as persistent light reactivity, actinic reticuloid, photosensitive atopic eczema, and photoallergic eczema.

Allergic Contact Dermatitis, Particularly Airborne Contact Dermatitis

Allergic contact dermatitis induced by externally applied or volatile/airborne substances acting as a contact allergens.

Atopic Eczema (**i.e.**, **When Provoked by Aeroallergens**)

Therapy

Usually topical corticosteroids are sufficient for symptomatic therapy. Most important is the future avoidance of the photoallergen and if needed sun-protective measures to prevent recurrences.

Prognosis

PACD is usually self-limited by strict avoidance of the photoallergen. Persistence of photosensitivity evolution of chronic actinic dermatitis is exceptional.

Cross-References

- ▶ Allergic Contact Dermatitis
- ▶ Atopic Dermatitis
- ▶ Emergent Allergies in Cosmetics
- ▶ Eyes and Eyelid, Contact Allergic Reaction On
- ▶ Fragrancy, Allergic Contact Dermatitis
- ▶ Photoallergic Contact Dermatitis
- ▶ Topical Corticosteroids

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Photopatch Test Baseline Series

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Synonyms

Baseline series of photoallergens; Basic photopatch test tray

Definition

The basic group of substances which can be recommended to detect the most relevant allergens in the workup of photoallergic contact dermatitis (PACD) by means of the technique of photopatch testing (PPT).

Choosing a Common Group of Agents for a Place and a Time

It is presumed that prevalence of photoallergy is low, but this assumption could be biased by worldwide underuse of PPT and also because an appropriate allergen selection for a standardized photopatch test series is not always available. In the same way than regular patch testing, a recommended list of standardized photoallergens has benefits both for clinical and for investigational purposes. However, studies about the most common photoallergens are much more limited than the investigation for conventional patch testing.

Two key aspects for recommending a PPT baseline series are that it should be based on

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photoallergens that are prevalent regionally (and it should be completed with additional allergens that are prevalent in specific parts of that region) and the list should be dynamic with removals or additions of allergens as they become discontinued or recently introduced in the market (Gonçalo 2011).

In the same way than regular patch testing for allergic contact dermatitis (ACD), in the diagnostic procedure of PACD, the PPT baseline series may be supplemented with extended series of PPT and the patient's own products.

The procedure and selection of photoallergens vary widely among dermatology centers and among countries, but attempts to standardize the method (selection of allergens and technique) have been developed since the 1980s (Jansén et al. 1982).

A milestone in the standardization of PACD diagnosis was the consensus methodology for PPT technique in Europe (Bruynzeel et al. 2004). It has recently been possible to choose 20 substances for a European photopatch test baseline series, thanks to a European multicenter PPT study, and take into account the known presence of those allergens in products (Table 1). The same European task force recommended 15 additional substances for an extended PPT series and published a list of 26 agents not considered suitable for inclusion in PPT regular series (Gonçalo 2013). Unfortunately, multicenter photopatch test studies are lacking for other regions of the world.

It is noteworthy that allergic contact dermatitis to PPT series is rare: in the European PPT study, 5 % of the subjects developed ACD reactions versus 19.4 % of PACD reactions.

Main Allergens

Here, the agents recommended for the European PPT baseline series (Table 1) and other photoallergens that could be suitable for baseline series in other parts of the world (Table 2) will be briefly exposed. The two most common allergen groups involved in photocontact dermatitis are sunscreen ultraviolet (UV) filters (mostly the organic UV-absorbing agents) and topically applied nonsteroidal anti-inflammatory drugs (NSAIDs). Other agents are medications of different groups, antiseptics, and fragrance ingredients.

UV Filters

Globally UV filters are the commonest photoallergens, so they have to be considered basic elements of PPT baseline series (Gonçalo 2011). There are several recent findings: older organic UV absorbers are the UV filters most frequently leading to PPT reactions, and among them octocrylene is an emergent photoallergen that together with benzophenone-3 is responsible for the majority of PTT reactions caused by UV filters in Europe (EMCPPTS Taskforce 2012). Benzophenone-3 was already included in basic PPT trays (in Europe and in North America), but octocrylene was not a photoallergen considered to be included in a basic PPT series until the European multicenter PPT study recommended it. Benzophenone derivatives have been historically the most frequent cause of photocontact allergy to sunscreens, although its use is declining.

Another finding of the European study was that octocrylene has potential for cross-reacting with benzophenone-3 and with ketoprofen. Although cross-reaction between ketoprofen and benzophenone-3 was known as they have similar molecular structures, the association between ketoprofen and octocrylene PACD has not been understood yet and could be related to special characteristics of ketoprofen that confer it a great potential for photoallergy.

Butyl methoxydibenzoylmethane has less risk of PACD than octocrylene and benzophenone-3, but it is the main UV filter included in sunscreens, and therefore, it is also one of the highest causes of PPT reactions.

Newer organic UV absorbers have produced few PPT reactions, but as their potential is unknown, they are recommended for PPT baseline series (seven included in the European PPT baseline series).

Also recommended for the European PPT baseline series are 4-methylbenzylidene camphor and

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Photopatch Test Baseline Series, Table 1 Allergens recommended for the European photopatch test baseline series (Adapted from Gonçalo et al. (2013))

Type of allergen	Name	Concentration	Comment
Older organic UV absorbers	Octocrylene	10 % pet	Emergent. The UV absorber most frequent cause of PPT reactions. Cross-reacts with ketoprofen and benzophenone-3
	Benzophenone-3	10 % pet	Also included in NA series
	Benzophenone-4	2 % pet	Also included in NA series (10 % pet)
	Butyl methoxydibenzoylmethane	10 % pet	Also included in NA series (5 % pet)
	Ethylhexyl methoxycinnamate	10 % pet	Also included in NA series (7.5 % pet). Few PPT reactions in EU
	Isoamyl-p-methoxycinnamate	10 % pet	Few PPT reactions in EU
	4-Methylbenzylidene camphor	10 % pet	Few PPT reactions in EU
	PABA	10 % pet	Also included in NA series (5 % pet). Rare presence in EU
Newer organic UV absorbers (Few PPT reactions could be explained by their novelty)	Methylene bis-benzotriazolyl tetramethylbutylphenol (Tinosorb M)	10 % pet	Most frequent ACD reactions
	Bis-ethylhexyloxyphenol methoxyphenyl triazine (Tinosorb S)	10 % pet	
	Drometrizole trisiloxane	10 % pet	
	Terephthalylidene dicamphor sulfonic acid	10 % aqua	
	Diethylamino hydroxybenzoyl hexyl benzoate	10 % pet	
	Ethylhexyl triazone	10 % pet	
	Diethylhexyl butamido triazone	10 % pet	
Topical NSAIDs	Ketoprofen	1 % pet	Most frequent cause of reactions in EU
	Etofenamate	2 % pet	Second cause of reactions in EU (unknown significance)
	Piroxicam	1 % pet	Also systemic photosensitivity
	Benzydamine	2 % pet	Topical use in mucosae Also systemic photosensitivity
Other drugs	Promethazine	0.1 % pet	Also included in NA series (1 % pet)

pet petrolatum, *aqua* water, *NA* North American, *EU* Europe

the cinnamates isoamyl-p-methoxycinnamate and ethylhexyl methoxycinnamate (the latter is also included in North American PPT Series, Chemotechnique Diagnostics).

In addition to the above agents that can be recommended globally, other sunscreen agents which are usually recommended for North American series and could be considered also suitable for European extended series are homosalate and ethylhexyl salicylate.

PABA (p-aminobenzoic acid) is a well-known photoallergen; although it is rare in Europe nowadays, it can be found in sunscreen products all over the world. It should be included in European PPT baseline series and globally in every basic series.

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Photopatch Test Baseline Series, Table 2 Allergens with secondary role in EU but suitable for other parts of the world (Data taken from the extended photopatch test series (Gonçalo et al. (2013)) and NA photopatch test series (Chemotechnique Diagnostics Catalogue))

Type of allergen	Name	Concentration	Comment
Older organic UV absorbers	Homosalate	10 % pet	Included in NA series (5 % pet)
	Ethylhexyl salicylate	10 % pet	Included in NA series (5 % pet)
	Methyl anthranilate	5 % pet	Included in NA series
	Benzophenone-10	10 % pet	Used outside EU
Topical NSAIDs	Dexketoprofen	1 % pet	Related to ketoprofen
Other drugs	Chlorpromazine	0.1 % pet	Neuroleptic
			Included in NA series
	Tribromosalicylanilide/ tribromsalan (TBS)	1 % pet	Historical photoallergen. Germicide. Included in NA series
	Triclosan	2 % pet	Extended use as preservative
			Included in NA series
	5-Bromochlorosalicylanilide	1 % pet	Historical photoallergen Germicide found outside EU
			Included in NA Series
	Hexachlorophene	1 % pet	Germicide included in NA series
	Tetrachlorosalicylanilide/ benzamide	0.1 % pet	Historical photoallergen Germicide found outside EU
	Fentichlor	1 % pet	Veterinary antimicrobial Almost absent in EU and the USA
	Bithionol	1 % pet	Veterinary antimicrobial
			Almost absent in EU and the USA
	Triclocarban	1 % pet	Antimicrobial for topic use
	Olaquindox	1 % pet	Historical photoallergen Germicide (veterinary) found outside EU
Fragrance ingredients	*Santalum album* (sandalwood oil)	2 % pet	Included in NA series
	6-Methylcoumarin	1 % pet	Included in NA series (1 % alc)
			Used outside EU
	Musk ambrette	5 % pet	Used outside EU

pet petrolatum, *aqua* water, *alc* alcohol, *NA* North American, *EU* Europe

Other possible constituents for PPT series could be mexenone (benzophenone-10) and phenylbenzimidazole sulfonic acid.

Topical NSAIDs and Other Drugs

Ketoprofen is the main allergen in Europe as has been shown by several studies from different countries. It is the allergen that caused most PPT reactions in the European multicenter PPT study. Etofenamate was the second cause, but its relevance usually is unclear. Benzydamine can elicit both PACD and systemic photocontact dermatitis and is included in the European basic PPT tray (EMCPPTS Taskforce 2012).

As prescription habits of topical NSAIDs are very different in other continents, recommendations for photopatch tests should be based in the regional prevalence of these drugs. Topical NSAIDs have been introduced in the USA later than in Europe, but its use as topical formulations may increase in the next years and they could be considered for PPT baseline series (Rietschel and Fowler 2008). Besides ketoprofen and benzydamine, other topical NSAIDs that could be included in a PPT baseline series for some countries are dexketoprofen, piketoprofen, ibuprofen, naproxen, and diclofenac.

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Drugs from other pharmacological groups that may be responsible for photoallergic reactions and are usually found both in Europe and North America are recommended for PPT baseline series: the topical antihistamine promethazine included in European PPT baseline series and the antiseptics triclosan and hexachlorophene and the neuroleptic chlorpromazine in North American series.

There are historical photoallergens, rarely used in Europe or the USA, but still available all over the world in the form of antiseptics and veterinary products, such as halogenated salicylanilides (tribromosalicylanilide is included in North American series), topical sulfonamides, halogenated antimicrobials (fentichlor and bithionol, the latter included in American series), olaquindox (has been banned in many countries), and triclocarban. Positive reactions to ketoprofen, fentichlor, and the salicylanilide have been suggested to be cross-reactions to a common metabolite (Victor et al. 2010).

Fragrance Ingredients

Some time ago, fragrance ingredients were the main cause of PACD (Rietschel and Fowler 2008). Photoallergens in perfumes that have been banned in Europe, but used elsewhere, are 6-methylcumarin (included in North American series) and musk ambrette. Sandalwood (or *Santalum album* oil) is not considered a usual photoallergen but is included in North American series.

Cross-References

► Photoallergic Contact Dermatitis

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Plants, Allergic Contact Dermatitis from

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P

Synonyms

Contact dermatitis; Plants

Definition

Plants can elicit allergic dermatitis either through direct skin contact or when touching the skin as small, aerogen distributed parts, which then provoke an airborne contact dermatitis. One of the most potent contact allergen of plants is urishiol, which can be found in poison ivy growing in North America. Up to 80 % of the US American population shows sensitization against urishiol, which is visible on the skin as brown

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discoloration and can result in severely blistering, erythematous skin reactions. Other relevant allergens of plants causing delayed-type hypersensitivity reactions are sesquiterpene lactones and terpenes from essential oils. Important exponents are composites (daisy family) and primroses. Also, plant extracts used in cosmetic products like chamomile or arnica can trigger an allergic contact dermatitis.

Cross-References

► Allergic Contact Dermatitis

Polidocanol: A Contact Allergen in Shampoo

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Synonyms

Contact dermatitis; Polidocanol

Definition

Polidocanol is a polyethylene glycol ether of lauryl alcohol, which is used as a nonionic emulsifier up to 4 % in rinse-off products such as shampoos, hair conditioners, and bath additives and up to 3 % in leave-on products like ointments and creams. It is considered as a week sensitizer for delayed-type hypersensitivity reactions but has been described as a potential contact allergen in hair shampoo.

Cross-References

► Allergic Contact Dermatitis
► Contact Dermatitis Due to Topical Drugs

p-Phenylenediamine Occupational Contact Dermatitis

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Synonyms

Hairdresser's contact dermatitis; p-Phenylenediamine (PPD) occupational contact dermatitis

Definition

PPD contact dermatitis is defined as cutaneous or systemic symptoms referred after a direct contact with several dyes, as blue or black ones, or other chemical products with this composition, needing several avoidance rules to prevent this illness.

Background

p-Phenylenediamine (PPD) is a very common allergen, because it is the main ingredient used in permanent hair color products in the market and the most allergenic one described in these products. Exposure to hair dyes has long been known as a significant risk factor for development of allergic contact dermatitis among the exposed population.

Dyes can be defined as colorants that are soluble in water and/or in organic solvent and have a particle size less than 0.01 μm and color substrates to which they have affinity. They have found widespread usage in industry as well as in many daily use products (see below). Hair dyes are one of the most frequently used hair cosmetics.

History

There are several references of hair dyes and its relationship with PPD. Hair dyeing with henna

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became increasingly popular during the nineteenth century, but was gradually replaced by PPD as the preferred hair dye in Europe (Wijnhoven et al. 2009). PPD was first described in 1863 by the German chemist Hofmann. Because of several allergic contact dermatitis cases due to PPD in hair dyes, its public use was banned in Germany in 1906 and later in several other European countries (Thyssen et al. 2008). In the 1930s, a clinical group suggested that PPD should be included in patch test standard series (Bonnevie 1939). Today, hair dyes are regulated in the European Union (EU) Cosmetic Directive such that PPD is allowed in a concentration of up to 6 % and toluene-2,5-diamine up to 10 %.

Classification

In order to know the importance of sensitization to PPD and to look for alternatives, hair dyes can be broadly classified into three main categories:

1. **Vegetable dyes:** Henna is the only available (and most used) vegetable hair dye. Natural henna takes several hours to be absorbed into the skin and imparts a brownish-orange color. Its active principle is lawsone (2-hydroxy-1,4-naphthoquinone). Black henna refers to the mixture of natural henna and PPD, which is added in order to decrease application time and to intensify the color, being the most typical reason of hypersensitivity after its use. In addition, other natural substances may be added to obtain different shades.
2. **Metallic dyes** usually contain lead acetate and several metallic salts, as bismuth, silver, copper, nickel, or cobalt, and they may be used to give a widespread range of colors. These tend to make hair brittle and impair subsequent permanent waving and are used infrequently.
3. **Synthetic organic dyes:** This group can be subclassified in two types (Clausen et al. 2006):
   a. **Direct hair dyes:**
      - **Temporary dyes** (color rinses) coat the hair and are removed by shampooing. The colorants are large, do not penetrate the cuticle layer, and are easily removed. If the hair is excessively dry or damaged, it may allow the pigment migration inside the hair shaft and thus a longer stay.
      - **Semipermanent dyes** are low molecular weight chemicals, which could penetrate the hair shaft and are retained for about 5–10 hair washings only. They are colored compounds and do not require any oxidation for their coloring action. The final color of each strand of hair depends on its original color and porosity, giving a more natural look with subtle variations compared to the permanent dye. Semipermanent dyes contain no, or very low levels of developer, peroxide or ammonia and are, therefore, safe for damaged or fragile hair.
   b. **Oxidative or permanent dyes** form the most important group of hair dyes and are most frequently incriminated in causing allergic contact dermatitis. They distinguish gray hair and change the original color of hair through a range of brown to black shades.

In the last years, several new hair colors have been introduced in the market (e.g., Vegetal biocolor), which claims to be free from the allergic adverse effects of PPD-based colors. The effectiveness in coloring the hair and potential adverse effects are still awaited.

Chemical Composition of Hair Dyes

Oxidative hair dyes are the most important group, as was commented before. These groups involve a mix of precursor along with coupler and oxidizing agent, which produce the resultant hair dye. The precursor most commonly used is PPD. The primary intermediates or precursors have little color on their own and are oxidized (possibly within hair shaft) by hydrogen peroxide to form colorless quinone diimines. The polymerized intermediate now in the presence of a coupler reacts to produce dyes; large, colored molecules are held within the hair shaft and are

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difficult to remove. Hair remains permanently colored.

The couplers are meta-substituted derivatives of aniline. Based on the color that they produce, couplers are divided in three major classes:

1. **Blue couplers** (1,3-diaminobenzene and its derivatives)
2. **Red couplers** (phenols and naphthols, such as 3-aminophenol, 5-amino-2-methylphenol, and 1-naphthol)
3. **Yellow-green couplers** (resorcinol, 4-chlororesorcinol, and benzodioxoles) (Corbett 1999)

PPD is a colorless intermediate chemical in the production of dyes and antioxidants. Production of a colored compound by PPD is a 3-step process.

Epidemiology

The prevalence is different between the countries and between the cities in the same country. Various studies have found the median prevalence of PPD positivity among dermatitis patients is near to 4.3 % in Asia, 4 % in Europe, and 6.2 % in North America (Thyssen et al. 2008; Sharma et al. 2004; Chan et al. 2001; Sharma and Chakrabarti 1998). These studies have demonstrated that these data change along the time, because Europe experienced a decrease in prevalence of PPD sensitization in the 1970s followed by a high prevalence ranging between 2 % and 6 %. The prevalence has remained high in North America. In Asia, the sensitization prevalence to PPD has ranged between 2 % and 12 % with relatively higher prevalence in Asian men than in women. This could be explained due to lack of adherence to the manufacturer's instructions by the consumer or hairdresser plus the application of a more concentrated final product, plus an increasing trend of hair dying and various cultural practices that may explain these differences between countries and between genders.

On the other hand, few authors have described three subgroups of patients sensitized to PPD: first was those with exposure to hair dyes, which included the hairdressers and the consumers (21.5 %); second group included those with occupational exposure to leather and textile industry (35 %); and the third (43.5 %) was unspecified group (Schnuch et al. 2008).

Focussing in occupational allergy and its epidemiology, working as a hairdresser is associated with an increased risk of contact allergy, the hairdresser being more sensitized to other allergens, with the risk increasing over the years. In one study, a clinical group found contact allergy to glyceryl monothioglycolate (GMTG) to be the commonest in patients currently or previously working as hairdressers. A steady decline in sensitization to PPD from 27.6 % to 17.2 % was observed during the period 1995–2002. A similar analysis during the period 2003–2006 showed ammonium persulfate (21.7 %) to be the most common sensitizer followed by PPD (18.1 %) and GMTG (7.5 %). In a review, the prevalence of contact dermatitis was seen in up to 80 % of hairdressers in smaller studies and 16.4 % in larger studies.

Pathogenesis

PPD-containing hair dyes would be expected to elicit allergic reactions in sensitized individuals, although there are several reasons that can stagger us. In one hand, hair dyes contain a large quantity of couplers that bind free PPD and thereby inhibit the potential sensitization of the product. On the other hand, the mixture of color gel and developer (oxidant) results in a rapid polymerization of the hair dye chemicals, which is washed within 30 min of application, thus having a minimal exposure time. One study used a dendritic cell (DC) activation assay in vitro and the local lymph node assay (LLNA) in vivo to assess sensitizing potential of PPD-containing hair dyes. It was observed that relevant DC activation and a positive LLNA test were induced by oxidized product of PPD but not by PPD itself and its acetylated products, indicating the immunogenic potential of PPD oxidation products (Aeby et al. 2009).

Several studies have been performed to estimate an exposure to precursors and couplers of

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oxidative hair dyes during and after hair dyeing. For this purpose, concentration of unconsumed precursors after color development has been measured, and up to 1.1 % of PPD has been found after color development. The Scientific Committee on Consumer Products (SCCP) has evaluated 11 combinations of precursors and couplers of oxidative hair dyes available in European market and determined the amounts of unreacted precursors and couplers in various formulations. It can be concluded that in spite of presence of couplers and oxidizing agents, significant amount of unreacted precursors is available on skin surface and in the dermis to act as allergen.

The second issue is regarding the sensitizing potential of these agents. One group evaluated the immunogenic potential of consumer-available permanent hair dyes in an animal model using a modified LLNA. It was observed that the application of the color gel both alone and mixed with the developer induced skin production of interleukin (IL)-1β, tumor necrosis factor-α, and IL-6 as well as infiltration and proliferation of T cells within the draining lymph nodes, with the inflammation being at least 20 % more severe with the mixture. Reducing the exposure time to the hair dye reduced the skin inflammation and cytokine production. Furthermore, it was demonstrated that the inflammatory response was at least 50 % higher when hair dye was washed away according to the manufacturer's protocol compared with mice exposed to 1 % PPD that was not washed away. Thus, the chemical composition within final mixtures is a more potent immune activator than 1 % pure PPD. These findings are in contrast to those referred before by Aeby et al.

These studies demonstrate that the pathogenesis is not clear enough, and more studies are needed to confirm the correct mechanism that produces this pathology.

Clinical Features

A PPD sensitization can be diagnosed more commonly as irritant contact dermatitis, allergic contact dermatitis, photocontact dermatitis, contact urticaria, and contact leukoderma, mostly in young to middle-aged individuals. Contact anaphylaxis due to hair dye has also been reported in several case reports. Clinical symptoms may begin within a few hours up to 1–2 days after the application of the dye with symptoms as itching, redness, papulation, and vesicles over the scalp, forehead, hairline margin, and around the eyelids (application zones).

The severity may vary from mild symptoms to moderate or severe symptoms. Lesions can also extend to the neck, upper chest, and upper arms and, rarely, may become generalized. It is very typical that men using hair dyes to color their beard and mustache may develop lesions over the face. Many patients complain of associated photosensitivity. Some patients may present with a predominant airborne contact dermatitis of the eyelids, retroauricular folds, and flexures, especially the cubital fossa. In severe cases, patients may present with prurigo-like lesions on the extensor aspect of extremities. Although less common, allergic reactions to hair dye also have been reported in children, being very typical in the age group of 12–15 years who get sensitized after an exposure to temporary henna tattoos, after receiving a hair dye, or after helping a hairdresser.

Rarely, adverse reactions to hair dye can present with a noneczematous morphology, as was reported as a lymphomatoid contact dermatitis to PPD-containing hair dye, which was proven on patch testing (Hospital et al. 2011). Other group diagnosed body dysmorphic syndrome in a hairdresser who despite having proven sensitivity to PPD continued to expose herself to the allergenic hair dyes while she was working and because she was dissatisfied with the appearance of her hair (Matterne et al. 2009). In other publication, one group found lenticular changes in 89 % of the 200 hair dye users compared to 23 % in the control group with an additional 7 % developing early presbyopia and concluded that hair dye is potentially toxic to human lens, an observation, which was confirmed on animal experiments. The prolonged effect of PPD exposure has been associated with renal impairment too, as was described after the evaluation of the long-term effects of PPD exposure in a group of

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72 hairdressers and observed high prevalence of renal impairment (14 %), proteinuria (26.4 %), and hematuria (41.1 %). Hypertension, skin changes, and bronchospasm were seen in 19.4 %, 38.9 %, and 22 % of females, respectively (Hamdouk et al. 2011).

Depigmentation due to contact sensitivity to PPD occurs over the scalp, extending beyond the hairline onto the neck. In one study, 864 patients presenting with chemical leukoderma were studied and found hair dyes to be the putative agent in 27.4 % of cases (Ghosh and Mukhopadhyay 2009). Other agents as hydrogen peroxide present in hair dyes may cause structural hair damage. Additives, such as pyrogallol and resorcinol, are other potential allergens. One group reported loss of eyelashes with the use of mascara containing PPD (Wachsmuth and Wilkinson 2006).

The oxidative capacity of hair dyes is a major cause of suicidal poisoning in India in recent years (Chrispal et al. 2010). Classically, hair dye poisoning presents with cervicofacial edema, severe rhabdomyolysis, and renal failure, being more dangerous if the symptoms are not controlled and not evaluated quickly.

Other atypical symptoms are related with the association of using hair dyes and malignancies. Although there are some reports of positive associations, based on current data, overall evidence linking personal use of hair dyes to various leukemia and myelodysplastic syndrome subgroups is weak, one cannot definitively rule out an association (Correa et al. 2000). Other group found a statistically significant increased risk (1.3–1.7 times) for bladder cancer among hairdressers, especially those in jobs for 10 years or more, but the results were confounded to an extent by large number of smokers in the population studied (Harling et al. 2010).

Diagnosis

The diagnosis of this allergic contact dermatitis is based in a clinical report focusing in the symptoms referred and the possible triggers. As was explained before, a reason-effect relationship has to be demonstrated to confirm the diagnosis.

To confirm a diagnostic hypothesis, epicutaneous patch test remains the gold standard to confirm the contact allergy to hair dyes. The allergenicity of PPD is related to oxidative processes on and in the skin. Patients with stronger reactions to PPD are significantly more likely to have a clear history of reacting to normal consumer hair dye. Individuals allergic to PPD have a significant frequency of simultaneous sensitivity to chemically related clothing dyes. Active sensitization from standard PPD patch testing although well known is not common.

One group has established an in vitro assay to diagnose PPD allergy. The procedure is based in freshly isolated peripheral blood mononuclear cells (PBMC) that are cultured with titrated concentrations of PPD with or without IL-2 supplementation, and cell proliferation is determined by [3H]-thymidine incorporation (Kneilling et al. 2010). Lymphocyte activation test (LAT) is used to detect PBMC cell proliferation specific to PPD, with at least 3.5-fold increase in [3H]-thymidine uptake required for a patient to be labeled as PPD allergic. PPD-LAT with IL-2 supplementation has demonstrated a sensitivity of 100 % and remains unresponsive in controls not sensitized to PPD and in those sensitive to other p-amino compounds.

Cross-Reactivity

It is very important to know the cross-reactivity between PPD and other substances. PPD may show cross-sensitization with other substances (Rietschel and Fowler 1995). Azo dyes, used in semipermanent and temporary hair dyes, ballpoint pen inks, and as coloring agent in foods and medications, may cross-react with PPD, and it has been assessed that 20–28.5 % of patients sensitized to textile dyes also have positive reactions to PPD. Exposure to azo dyes from shoes may cause foot dermatitis and cross-sensitization to PPD. However, the primary cause of sensitization in dermatitis patients in general is most often with PPD, whereas primary sensitization to azo dyes is much less common.

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Drugs like benzocaine and procaine, sulfonamides, sulfones, sulfa drugs, para-aminobenzoic acid, and para-aminosalicylic acid cross-react with PPD.

Treatment

In order to decrease the burden of disease, use of alternative natural dyeing agents among consumers and use of barrier neoprene gloves among hairdressers should be encouraged apart from severe legislation to reduce the amount of PPD reaching the consumer.

The causative hair dyes should be withdrawn. Regular use of sunscreens over sun-exposed areas with SPF 30 should be advised to those who manifest photosensitivity. Additional protection with use of appropriate clothing and wide brim hats is helpful. Symptomatic relief can be achieved with the use of topical steroids in lotion formulation, although care should to be taken to avoid superpotent steroids on the face and their prolonged use (more than 10–14 days) to prevent their adverse effects. In severe cases, short course of systemic steroids may be required. Systemic antihistamines to counter the itching may be needed. Pure henna can be substituted for hair dyes. Hydroxyethyl-p-phenylenediamine sulfate (HPPS), itself a known sensitizer, has been valuated as a dyeing alternative for patients who are sensitive to PPD. In a study, 40 of 216 (19.9 %) patients reacted to 1 % PPD, whereas only 2/216 (0.9 %) showed a positive reaction to 1 % HPPS and 2.3–2 % HPPS.

To avoid allergic reactions to hair dyes, an open test (or dab test) is recommended 48 h before the hair coloring procedure. One group studied the sensitivity and specificity of the consumer open skin allergy testing to predict the possibility of contact dermatitis to hair dyes (Krasteva et al. 2005). Test products containing increasing concentrations of PPD (0.1, 0.5, 1.0, or 1.5 %) were applied to 34 PPD-positive hair dye-allergic individuals and to 49 nonallergic control subjects. Allergic reactions were elicited in all PPD-positive subjects, whereas none occurred in control PPD-negative subjects. It can be concluded that the skin allergy test is a suitable tool for the secondary prevention of contact allergic reactions to hair coloring products.

Recommended strategies for the prevention of hand dermatitis in hairdressers include improved education, appropriate glove use, and the application of after-work moisturizing creams. One group conducted a population-based study involving 193 trainee hairdressers and 184 practicing hairdressers to assess their knowledge of skin hazards, the skills they practiced, and the frequency of glove use. Knowledge of skin hazards was poor in both groups. The use of gloves was inadequate, particularly when performing work. Other groups investigated the permeation behaviors of 2 % p-aminophenol (PAP), 2 % m-aminophenol (MAP), 2 % o-aminophenol (OAP), and 4 % PPD with disposable natural rubber latex (NRL) gloves, disposable polyvinylchloride (PVC) gloves, and neoprene (NP) gloves. Breakthrough times were 4 h for NRL and PVC gloves and more than 8 h for NP gloves, which was not hastened with the use of hydrogen peroxide.

Based on these observations, it can be concluded that disposable NRL gloves and disposable PVC gloves should not be used repeatedly for handling the hair dye products.

Recommendations

Based on cross-reactivity and in order to avoid the exposition and symptoms, patients have to know the localization of p-phenylenediamine:

- Hairdressers: It can be read in permanent and nonpermanent dyes.
- Clothes and leather: It can be found in cloth dye, tights, leather, shoe shiners, etc.
- Pigments: It can be found in several dark beauty products, as, for example, eye shadow; India ink; several dyes (methylene blue, safranin); azo dyes; photo developer and lithography; temporally tattoos; X-ray fluids; and as a blood reactive in blood samples (chlorhydrate).

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- Antioxidants: It can be found in rubber and plastics, lubricant oil and petrolatum, oil derivatives (as gasoline), etc.

On the other hand, patients have to know several advices to avoid p-phenylenediamine allergy:

- If patients need a hair dye, they have to require p-phenylenediamine-free products and its derivatives.
- p-Phenylenediamine is labeled with other synonyms, as follows: 1,4 benzenediamine, paraphenylenediamine (PPD or PPDA), p-aminoaniline, 1,4-phenylenediamine, p-diaminobenzene, disperse dyes and azo dyes, anthraquinones, black rubber products, diaminodiphenylmethane, 2,4-diaminoanisole, ortho-aminophenol, PABA, p-aminosalicylic acid (PAS), p-aminodiphenylamine, p-toluendiamine, benzocaine, and other local anesthetics, sulfonamides, sulfones, and parabens.
- Nitrile or vinyl gloves can avoid direct contact in hairdressers, and they have to use them always.
- Patients do not have to handle India ink, black rubber products, and skin or cloth inks, unless they do not contain p-phenylenediamine.
- Patients have to avoid dark clothes.
- Patients do not have to use solar filters with PABA and/or benzocaine and/or sulfonamides because they can react to these substances.
- In work situations, patients have to say they need products without p-phenylenediamine, and they have to know the product composition they use, in order to avoid them and/or to protect correctly to avoid symptoms.

Cross-References

- ▶ Allergen Avoidance: Avoidance Strategies for Skin Allergies
- ▶ Allergic Contact Dermatitis
- ▶ Contact Allergy to Black Henna Tattoos
- ▶ Contact Allergy to Hair Dyes
- ▶ Emergent Allergies in Cosmetics
- ▶ Eyes and Eyelid, Contact Allergic Reaction On
- ▶ Photoallergic Contact Dermatitis

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Predictive Value Model for Laboratory Tests: Diagnostic Sensitivity, Diagnostic Specificity, Positive and Negative Predictive Value, Efficiency, Likelihood Ratio ([positive and negative]), Incidence and Prevalence

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Synonyms

Diagnostic sensitivity; Diagnostic specificity; Likelihood ratio (positive and negative)

Definition

The *predictive value model for laboratory tests* is an analytical data-based system for documenting the overall performance of a diagnostic laboratory test in terms of its ability to accurately distinguish the presence of a disease state with a positive test result from the absence of a disease state with a negative test result.

Introduction

The differential diagnosis of a disease state begins with a thorough evaluation of a patient using a physical examination and clinical history (Galen 1982). To confirm or support a suspicion of a disease state, a laboratory test is often performed. The analyte that is measured in the test should provide information about the disease state being evaluated. To be considered useful to the diagnostic process, a laboratory test needs to be able to detect or confirm the disease state or disorder, provide information about the pathological process, and/or quantify the extent of the abnormality. An abnormal test result must have a high degree of association with the disorder or disease state being examined. These are considered true positives. Alternatively, a test result in an otherwise in a normal range for healthy individuals needs to have a high degree of association with the absence of the disease state or disorder. These results are considered true negative. The *predictive value model of laboratory tests* as applied to health and diseased populations has been developed to provide the clinician with an indication of clinical utility of a test in the diagnosis of a disease state or disorder (Chen et al. 2012; Vihinen 2012; Villalta et al. 2012).

Laboratory Assay Efficiency

The predictive value model uses a number of terms to define how well a positive result from the test detects a clinically definable disease state and how effectively a negative test result identifies the absence of that disease. The overall

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efficiency of a laboratory test is computed as the percentage of patients that are correctly identified by the diagnostic test result as having the particular disease or not having the disease. An efficiency of 100 % indicates that all the patients with a positive result present with the disease and all the patients with a negative result have no evidence of the disease. Laboratory test **efficiencies** approaching 100 % are the goal of every assay manufacturer; however, this target is rarely achieved. Assay **efficiency** is defined by analyzing specimens in the assay system being studied that are collected from patients with a clearly defined disease state.

Predictive Value Model for Laboratory Tests: Diagnostic Sensitivity, Diagnostic Specificity, Positive and Negative Predictive Value, Efficiency, Likelihood Ratio ([positive and negative]), Incidence and Prevalence, Table 1 Two-by-two predictive value model for a laboratory test

	Disease Positive (number)	Disease Negative (number)
Test Positive (number)	True positive (TP)	False positive (FP) Type 1 Error
Test Negative (number)	False negative (FN) Type 2 Error	True negative (TN)

Diagnostic Sensitivity and Specificity

Terms that are commonly used to assess the efficiency of the test include its **diagnostic sensitivity** and **diagnostic specificity**. The ability of a diagnostic test to accurately report a positive result in the presence of disease or define a **true positive** is the **diagnostic sensitivity** of a laboratory test. It reports the frequency of a positive test result when the disease is present. In contrast, the ability of a diagnostic test to produce a negative result in the absence of disease which is considered a **true negative** result is the **diagnostic specificity** of a test. It provides a measure of the frequency of negative diagnostic tests when the disease is not present. These computations are reflected in the two by two correlation table (see Table 1) in which the number of positive test results are categorized between subjects who have disease and those without disease. Additionally, the numbers of negative tests are categorized between subjects who have disease and those without disease. A type 1 error or **false positive** result occurs when a healthy individual without disease has a positive test result. A type 2 error or **false negative** result occurs when a diseased individual has a negative test result (Leeflang et al. 2012). To develop the dataset to compute this two-by-two table (Table 1), the disease state in the patient and the positive/negative cutpoint of the assay both need to be clearly defined.

Using a more formulaic approach, the **diagnostic sensitivity** or test positivity in disease = [True positives/(True Positives + False Negatives)] × 100. In the absence of false negative results, the diagnostic sensitivity is 100 %. Moreover, **the diagnostic specificity or t**est negativity in health = [True Negatives/(False Positives + True Negatives)] × 100. In the absence of false positive test results, the diagnostic specificity is 100 %. The probabilities of these outcomes for any defined population can be calculated and expressed as **predictive values**. The **positive predictive value** of a diagnostic test is the percentage of patients with positive test results that have disease. This is computed as [True positives/(True positive + False positive)] × 100. In contrast, the **negative predictive value** is the percentage of patients with negative test results who are not diseased. This is computed as [True negatives/(True negatives + False negatives)] × 100. Thus, the test's overall **efficiency** or percentage of patients who are correctly classified by the test result as having disease or not having disease can be computed as: [True positive + True negative]/[True positive + False positive + True negative + False negative] × 100.

Likelihood Ratio

An alternative approach to assessing the performance of a diagnostic laboratory test is the use of

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a **likelihood ratio** (McGee 2002). This ratio uses the "diagnostic sensitivity" and "diagnostic specificity" of the test to determine whether a test result will usefully alter the probability of identifying if that disease state or condition exists in a study population. There are two forms of the likelihood ratio. The **likelihood ratio positive** (LR+) is used for positive test results and the **likelihood ratio negative** (LR−) is used for negative test results. The **likelihood ratio (positive)** defines the probability of a person with the disease testing positive divided by the probability of a person without the disease testing positive. The **likelihood ratio (negative)** report the probability of a person with the disease testing negative divided by the probability of a person without the disease testing negative. A **likelihood ratio** greater than 1 indicates the test result is associated with the disease, while a likelihood ratio less than 1 indicates that the result is associated with absence of the disease. If the test has likelihood ratios close to 1, it has little practical significance since the posttest probability is close to the pretest probability, and thus it may be used for diagnostic purposes but not screening purposes.

Using a more formulaic approach, the **likelihood ratio positive** is the probability of a person with the disease testing positive divided by the probability of a person without the disease testing positive. This is computed as LR + = (diagnostic sensitivity)/(1 − diagnostic specificity) = true positives/false positives. Another way of computing the likelihood ratio positive is

LR + = [[True positives/(True Positives + False Negatives)]/[1 − [True Negatives/(False Positives + True Negatives)]]]

The **likelihood ratio negative** is the probability of a person with the disease testing negative divided by the probability of a person without the disease testing negative. This is computed as LR− = (1 − diagnostic sensitivity)/(diagnostic specificity) = true positives/false positives. Alternatively, the likelihood ratio negative is

LR− = [1 − (True positives/(True Positives + False Negatives))]/[True Negatives/(False Positives + True Negatives)]

Predictive Value Model for Laboratory Tests: Diagnostic Sensitivity, Diagnostic Specificity, Positive and Negative Predictive Value, Efficiency, Likelihood Ratio ([positive and negative]), Incidence and Prevalence, Table 2 Changes in the positive predictive value of a laboratory test with a 95 % diagnostic sensitivity and specificity as the prevalence of disease changes*

Prevalence of disease (%)	Positive predictive value (%)
1	16.1
2	27.9
5	50.0
10	67.9
15	77.0
20	82.6
25	86.4
50	95.0

*Reproduced from Galen and Peters 1986

Incidence and Prevalence of a Disease

Incidence is the rate of new (or newly diagnosed) cases of the disease reported in a defined period of time, typically a year. **Prevalence** is the actual number of cases with the disease either during a period of time (**period prevalence**) or at a particular date in time (**point prevalence**). If there is a change in the prevalence of the disease in the population under study, it will result in a marked change in the predictive value of a diagnostic test. For example, a particular test for a disease will have a higher predictive value if it is applied to a population with a higher prevalence of that disease. In other words, the number of false positive and false negatives will vary between populations having different prevalence rates of the disease being studied. This concept is illustrated in a hypothetical clinical study that evaluates a new antibody test for allergic disease (rhinitis). The test has a **diagnostic sensitivity** and **diagnostic specificity** for rhinitis of 95 % such that 95 % of diseased patients have a positive test and 95 % of non-diseased patients have a negative test. If the prevalence of rhinitis in a study population is 5 %, then 50 % of the patients with a positive of the antibody test (**positive predictive value**) would have rhinitis, and the remaining would be false positives (See Table 2).

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Predictive Value Model for Laboratory Tests: Diagnostic Sensitivity, Diagnostic Specificity, Positive and Negative Predictive Value, Efficiency, Likelihood Ratio ([positive and negative]), Incidence and Prevalence,

Table 3 Illustrative evaluation of a diagnostic test with low disease prevalence of 5 %*,**

	Disease Positive (number)	Disease Negative (number)	
Test Positive (number)	True positive TP = 48	False positive FP = 47 Type 1 Error	Positive Predictive Value = TP / (TP + FP) = 48 / (48+47) = 50.5%
Test Negative (number)	False negative FN = 2 Type 2 Error	True negative TN = 903	Negative Predictive Value = TN / (TN + FN) = 903/(903+2) = 99.8%
	Sensitivity TP / (TP + FN) = = 48 / (48+2) = 96%	Specificity TN / (FP + TN) = = 903 / (903+47) = 95%	

*** Disease prevalence: [50 positive cases] / [1000 total cases] = 5%**

** Reproduced from Galen and Peters, 1986

Likelihood ratio positive = sensitivity / (1 − specificity) = 96% / (1 − 95%) = 19.2
Likelihood ratio negative = (1 − sensitivity) / specificity = (1 − 96%) / 95% = 0.04

Illustrative Examples of Predictive Value Assessment for a Diagnostic Test for Diseases with Different Prevalence Values

Tabels 3 and 4 provide hypothetical data for two diagnostic tests. In Table 3, the prevalence of the disease is low (5 %) with a high-diagnostic sensitivity and specificity of ∼95 %. In Table 4, the prevalence of the disease increases to 50 % and the positive predictive value of the test increases from 50.5 % to 95 %.

The test presented in Table 3 is marginal at confirming the disease with a **positive predictive value** of 50.5 %, but when the test is positive, it correctly identifies 95 % of all individuals with the disease and has a **diagnostic sensitivity** of 96 %. As a screening test, a negative result would be good at reassuring that an individual does not have the disease as evidenced by a **negative predictive value** of 99.8 %. As an initial screening test, it would correctly identify 95 % of those who do not have disease and display a **diagnostic specificity** of 95 %.

By increasing the prevalence of the disease in population to 50 % as illustrated in Table 4, the ability of the test to confirm disease improves with a **positive predictive value** of 95 %, while still correctly identifying 95 % of all individuals with the disease (**diagnostic sensitivity**). As a screening test, a negative result will continue to effectively identify individuals without disease with a **negative predictive value** of 95 %. Moreover, if used as an initial screening test, it will correctly identify 95 % of those who do not have disease (**diagnostic specificity**). In both cases (Tables 3 and 4), the likelihood ratios indicate that a positive test result adds value in identifying a person with disease, and a negative test result is associated with absence of the disease.

Summary

A laboratory test needs to provide diagnostically useful information by (a) detecting or confirming a disorder when the clinical history and other approaches are not effective, (b) defining a pathological process to suggest an optimal management strategy, or (c) quantifying an abnormality that has been already identified. To be useful, an abnormal or positive laboratory test must have a high association with a particular disorder. The diagnostic performance of an analytical test is

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Predictive Value Model for Laboratory Tests: Diagnostic Sensitivity, Diagnostic Specificity, Positive and Negative Predictive Value, Efficiency, Likelihood Ratio ([positive and negative]), Incidence and Prevalence,

Table 4 Illustrative evaluation of a diagnostic test with high prevalence *,**

	Disease Positive (number)	Disease Negative (number)	
Test Positive (number)	True positive TP = 475	False positive FP = 25 Type 1 Error	Positive Predictive Value = TP / (TP + FP) =475/ (475+25) = 95%
Test Negative (number)	False negative FN = 25 Type 2 Error	True negative TN = 475	Negative Predictive Value = TN / (TN + FN) = 475 / (475+25) = 95%
	Sensitivity TP / (TP + FN) = = 475 / (475+25) = 95%	Specificity TN / (FP + TN) = =475 / (475+257) = 95%	

*** Disease prevalence: [500 positive cases] / [1000 total cases] = 50%**
** Reproduced from Galen and Peters, 1986

Likelihood ratio positive = sensitivity / (1 − specificity) = 95% / (1 − 95%) = 19
Likelihood ratio negative = (1 − sensitivity) / specificity = (1 − 95%) / 95% = 0.05

judged based on its ability to accurately identify a disease state when it is present and rule out a disease state when it is not present. The relevant clinical state ideally needs to be clearly definable when evaluating the diagnostic performance of a laboratory test. When applying a diagnostic test to the evaluation of a population for a particular disease, only some of the individuals which have the disease will have negative tests (false negatives), while others without the disease will have positive tests (false positives). The probabilities of these outcomes can be computed for any defined population and expressed as predictive values. The values discussed in this text to judge the performance of a diagnostic test include its **diagnostic sensitivity**, **diagnostic specificity**, the **positive and negative predictive values**, the **test efficiency**, and the **likelihood ratio (positive and negative)**.

Cross-References

- ▶ Assay Performance Parameters
- ▶ Diagnostic Food Challenges
- ▶ Exercise Challenge
- ▶ Exhaled Nitric Oxide
- ▶ Food Allergies, Diagnostic Testing
- ▶ IgE Testing
- ▶ Mannitol Challenge
- ▶ Methacholine Challenge
- ▶ Methods (In Vitro and In Vivo): Multiplex Immunoassay Systems
- ▶ Methods (In Vivo) Provocation Tests (Nasal Challenge, Bronchial Challenge, Food Challenge)
- ▶ Methods (In Vivo): Skin Test (Intradermal, Puncture)
- ▶ Single-Plex Immunoassays and Autoanalyzers
- ▶ Testing: High-Resolution Chest Computed Tomography Scan

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Preservatives Contact Allergy

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Synonyms

[(o-Carboxyphenyl)thio] ethylmercury sodium salt; 5-Chloro-7-iodoquinolin-8-ol; Betacide; Biocides contact allergy; Bonomold; Butyl-3-iodo-2-propynylcarbamate; Carbamic acid; Chemoside; Chinoform; Chloroiodoquine; Cliochinolum; Disinfectants contact dermatitis; E210–219; Ethyl (2-mercaptobenzoato-S) mercury sodium salt; Formalin; Germall™ Plus; Glycacil™; IBP; IODOCARB™; Iodochlorhydroxyquin; Iodochlorhydroxyquinoline; IPBC; Kathon 886™; Kathon™; MCI/MI; Mercurothiolate; Merthiolate; Methanal; Methyl aldehyde; Methylchloroisothiazolinone/methylisothiazolinone; Methylene oxide; Morbicid acid; Nipagin; Oxymethylene; Propagin; Sodium ethylmercurithiosalicylate; Solbrol; Tegosept; Thiomersalan; Thiomersalate; Vioform

Definition

Preservatives are substances that protect against microbial proliferation. They are used in foods, but also in body care preparations, household goods, and industrial products. They are one of the main causes of allergic contact dermatitis.

Introduction

A preservative is a naturally occurring or synthetically produced substance that is added to products such as foods, pharmaceuticals, paints, biological samples, wood, etc. to prevent decomposition by microbial growth or by undesirable chemical changes. They inhibit growth of bacteria and fungi. An ideal preservative should be active only against microbial organisms, without adverse effects (toxic, allergic, or irritant reactions) in people in contact with them.

Many countries limit the concentration of preservatives by regulations and require preservatives to be listed on the package.

People who become allergic to preservatives can have either local or generalized cutaneous eruptions or mucosal involvement (mainly ocular or oral).

Historical Background

Preservatives were introduced as early as the nineteenth century for topical uses.

The first contact allergy epidemic due to preservatives was observed during the 1960s in Western countries and was caused by formaldehyde in cosmetics. This epidemic led to a marked decrease in the use of formaldehyde in cosmetics, but at the same time, the use of formaldehyde releasers in these products has increased (Svedman et al. 2012).

The introduction of Kathon CG (5-chloro-2-methyl-4-isothiazolin-3-one (MCI) + 2-methyl-4-isothiazolin-3-one (MI)) in the 1980s was responsible of epidemics of contact dermatitis in different European countries.

In the mid-1980s, a marked increase in allergy to another preservative, Euxyl

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K 400 (methyldibromoglutaronitrile – MDBGN – and phenoxyethanol), was detected, leading to changes in the European Cosmetics Directive in 2005, banning first the use of MDBGN in stay-on products and later on in rinse-off products.

Due to the increasing use of isothiazolinone-based preservatives in recent years, a significant rebound of reported contact allergy to these products has been reported.

Prevalence

Studies carried out in eight European countries compared the annual percentage of positive patch test reactions to preservatives along the period 2001–2008 (Svedman et al. 2012):

- Paraben mix remained the preservative with the lowest level of contact allergy (0.5–1 %).
- The frequencies of contact sensitivity to other preservatives such as quaternium-15 (1–1.5 %), imidazolidinyl urea (0.5–1 %), and diazolidinyl urea (0.8–1.4 %) showed no relevant changes when compared with previous data.
- The higher frequencies (above 2 %) were reported with formaldehyde (2–25 %), MDBGN (3–4 %), and MCI/MI (1.7–2.7 %).

A study in the USA compared the prevalence of positive reactions to preservatives in patch-tested individuals between 1996 and 2002 (Lundov et al. 2009):

- Paraben sensitization decreased from 1.7 % in 1996–1998 to 0.6 % in 2001–2002.
- The prevalence of patch test positives from formaldehyde and quaternium-15 was about 9 % for each preservative along the period.
- Prevalence of contact allergy to diazolidinyl urea ranged between 2.7 % and 3.7 % of patch test positivities.
- Contact allergy to imidazolidinyl urea remained stable around 2 % in this period of time.

Benzalkonium Chloride

It is a quaternary ammonium compound that has been increasingly incorporated into many products such as preservatives and disinfectants (personal care products, ophthalmologic preparations, antifungal treatments, toothpastes, etc.).

Benzalkonium chloride is a well-established skin irritant and can exacerbate preexisting dermatoses. Allergic sensitivity due to this product is infrequent (Dao et al. 2012).

Clioquinol

Clioquinol is a quinoline compound with antibacterial and antifungal properties. It is found in topical preparations to treat skin infections (infected eczema, athlete's foot, and other fungal infections). It is often used in combination with topical corticosteroids. It can be also found in eye and ear preparations (Andersen et al. 2011).

It is not a strong allergen. It has been mainly related to stasis dermatitis and otitis externa. Oral administration of clioquinol has resulted in a generalized eruption in individuals allergic to this compound. The prevalence of contact allergy is about 0.7 %. Irritant reactions due to clioquinol have also been described.

Cross-reactions with other quinolones as chlorquinaldol are not common.

Ethylenediamine

It is a potent sensitizer used in topical medications (antibiotic/steroid creams) due to chemical stabilizing properties. It is rarely found in cosmetic and toiletries.

Ethylenediamine is also an ingredient of aminophylline that was commonly used in the treatment of asthma and other respiratory problems in the past. Other medications where it is found include some antihistamines (hydroxyzine hydrochloride, cetirizine, piperazine, cyclizine).

Occupational exposure to ethylenediamine (Andersen et al. 2011) has been described with:

- Floor polish removers
- Epoxy hardener
- Coolant oils
- Rubber industry

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– Dye industry
– Insecticides
– Animal feed supplements
– Synthetic waxes
– Health-care workers (nurses, laboratory technicians, etc.)

Ethylenediamine is a cause of allergic contact dermatitis. Damaged skin is more readily sensitized than normal intact skin and ethylenediamine allergy has been described as a worsening of an original eczema that was being treated with creams containing it.

Systemic administration either through inhalation or oral use of preparations containing ethylenediamine (aminophylline, piperazine) can cause exacerbations of generalized erythroderma or eczematous eruptions (systemic contact dermatitis).

Euxyl K 400

Euxyl K 400 (Schülke & Mayr GmbH, Norderstedt, Germany) was first introduced in consumer products in 1985 in Europe and 5 years later in the USA. It is a 1:4 mixture of methyldibromoglutaronitrile (MDBGN) and phenoxyethanol.

It is a preservative equally effective against bacteria, fungi, and yeast, used in both cosmetics and industrial products.

Although originally appeared to have low sensitizing potential, MDBGN has become an important source of contact allergy (Aakhus and Warshaw 2011).

Phenoxyethanol has only rarely been cited as source of contact dermatitis (aqueous cream, vaccines, and medical gauzes) and contact urticaria.

Formaldehyde

It is a ubiquitous preservative and both a potent contact sensitizer and a primary irritant. There are other preservatives called formaldehyde releasers (FR) or donators that release formaldehyde by hydrolysis in the presence of water.

The main source of domestic formaldehyde exposure is cosmetics (fingernails polishers, hardeners, etc.) (78 %) (Lundov et al. 2010).

Other non-occupational uses of formaldehyde are:
– Toiletries (shampoos, antiperspirants, deodorants, mouthwashes)
– Household cleansers, disinfectants, and polishes
– Paper products
– Clothes
– Medications: wart remedies, root canal preparation disinfectants, etc.

There are hidden sources of formaldehyde at home and these exposures may explain some apparently non-relevant positivity to this preservative in patch tests.

Formaldehyde has industrial uses in textiles treated with formaldehyde resins (rare cause of sensitization), metalworking fluids, paints, building materials (urea-formaldehyde glue or adhesive), and embalming fluids. Occupational formaldehyde allergy (Aalto-Korte et al. 2008) was formerly common and occurred in:
– Metaworkers
– Hairdressers
– Masseurs
– Health-care workers
– Cleaners
– Cosmetologists
– Painters
– Photographers
– Technicians
– Maintenance and housekeeping personnel
– Workers using protective creams, detergents, and liquid soaps

Repeated or prolonged exposure may cause hypersensitivity and then allergic contact dermatitis. Formaldehyde allergy has been associated with hand dermatitis. Textile allergy due to formaldehyde affects parts of the body where there is greatest friction (inner thighs, gluteal folds, and backs of the knees).

Exposition to formaldehyde gases may cause affectation of mucous membranes (in eyes, nose, and throat), skin rashes, dyspnea, wheezing, etc.

There are also described immediate allergic and nonallergic reactions due to exposition to it.

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Formaldehyde is difficult to avoid. It is widely distributed in the environment and many products may contain small amounts.

Formaldehyde Releasers

This group of preservatives included:
- Imidurea (imidazolidinyl urea)
- Diazolidinyl urea
- Bronopol™ (2-bromo-2-nitropropane-1,3-diol)
- Quaternium-15
- Dimethyl-dimethyl (DMDM) hydantoin
- Benzylhemiformal
- 5-Bromo-5-nitro-1,3-dioxane
- Sodium hydroxymethylglycinate
- Bioban™
- 1,6-Dihydroxy-2,5-dioxahexane
- Forcide® 78
- N,N_-Methylenebis(5-methyloxazolidine)
- 4,4_-Methylenedimorpholine
- Tris(*N*-hydroxyethyl)hexahydrotriazine
- Tris(hydroxymethyl)nitromethane

They are used in cosmetics and technical products and are often concealed by a multitude of trade names or synonyms (de Groot et al. 2009).

Approximately 20 % of cosmetics and personal care products in the USA contain a formaldehyde releaser (1/6 for stay-on cosmetics, 1/4 for rinse-off products) (de Groot et al. 2010).

Like formaldehyde, these substances can trigger allergic skin reactions. An allergic reaction to a formaldehyde releaser can be caused either by the released formaldehyde or by the formaldehyde releaser itself. Except for Bronopol™ the prevalence of formaldehyde allergy in formaldehyde releaser-sensitized patients was high (34–79 %) (Lundov et al. 2010).

Formaldehyde releasers, such as diazolidinyl urea, imidazolidinyl urea, and quaternium-15, are almost uniquely used in cosmetics, whereas Bronopol™ and other releasers are mainly used in non-cosmetic products (Aalto-Korte et al. 2008, Anderson BE 2007).

Iodopropynyl Butylcarbamate (IPBC)

It is a water-based preservative of the carbamate chemical family. It has been used for years as a preservative in water-based paints and metal-working fluids and as a wood preservative. More recently it has been used as a preservative in cosmetics products. IPBC is effective against a wide variety of microorganisms.

It is safe when used at concentrations less than 0.1 %, but their widespread use in cosmetics has led to an increase in the reported cases of contact allergy. The dermatitis affects hands and arms, and in some cases a generalized dermatitis might develop (Badreshia and Marks 2002).

Kathon CG™

It is a preservative (Rohm and Haas, Philadelphia) with two active ingredients: 5-chloro-2-methyl-4-isothiazolin-3-one (MCI) and 2-methyl-4-isothiazolin-3-one (MI) with a 3:1 ratio.

Kathon CG™ has been used for a long time. During the 1980s, a European "epidemic" of contact dermatitis caused by MCI/MI occurred, with sensitization rates of up to 5.0 %. Despite changes of recommended concentrations, sensitization to MCI/MI remains at a high prevalence of 2 %. MI has also increasingly been used alone, without MCI, or in combination with other preservatives.

This product and its components are used in cosmetics and skin care products, as well as in household and industrial products.

Contact allergy to both compounds is well known, with MCI being regarded as the stronger allergen. Sensitization to MI is mainly thought to be acquired as an immunological cross-reaction after sensitization to MCI. However, isolated sensitization to MI also occurs (Geier 2012).

Parabens

These amino benzoic acid esters include:
- Methylparaben
- Ethylparaben

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- Propylparaben
- Butylparaben
- Isobutyl paraben
- Isopropyl paraben

Parabens are popular preservatives because they are colorless, odorless, stable, and inexpensive. They are the most widely used preservatives in foods, drugs, and cosmetics. Generally two or more parabens occur together in the same product and are associated with other biocides (Andersen et al. 2011). Parabens are more active against Gram-positive than Gram-negative bacteria and even more active against yeasts and molds than against bacteria.

Parabens are irritants, and their use for parenteral or ophthalmic preparations should be avoided. They are relatively weak allergens. Despite numerous reports of delayed hypersensitivity related with their topical use, confirmed reactions are fairly uncommon. Contact dermatitis due to parabens affects mainly elderly patients with long-lasting treatments (stasis dermatitis, leg ulcers, etc.) (Uter et al. 2013). Cross-reactions between the four paraben esters are common.

A recent final report on the safety assessment of parabens as used in cosmetic products concluded that they are very safe (Anonymous 2008).

The term "paraben paradox" was used in relation with leg ulcer patients with paraben allergy that tolerate paraben-preserved cosmetics on healthy skin (Fisher 1979).

Other para compounds (benzocaine, PPD, sulfonamides) can cross-react with parabens, but this cross-sensitization is rare.

Immediate reactions due to parabens (contact and systemic urticaria) have also been reported.

Thimerosal

Thimerosal is a preservative with two sensitizing moieties: mercury and thiosalicylic acid. This antiseptic has bactericidal and fungicidal actions. It is used in merthiolate tincture and as a preservative (cosmetics, vaccines, toxoids, contact lens solutions, and eye, ear, and nose drops, etc.)

The relevance of a positive patch test to thimerosal is very difficult to establish (Breithaupt and Jacob 2008). Their use has declined in recent years (still present in eyedrops, vaccines), but it is a potent sensitizer, particularly in topical products.

Localized allergic reactions may occur in the skin or mucosa of sensitive individuals. When it is an injectable thimerosal-containing preparation (vaccines), redness and swelling at the injection site may appear. The reactions are usually mild.

If thiosalicylic acid moiety is the culprit of the sensitization, the patient should avoid the use of piroxicam, a nonsteroid anti-inflammatory drug with cross-sensitization with this preservative.

Clinical Manifestations

Preservative allergy is more common in women than in men. It results in dermatitis in areas exposed to the responsible chemical. For example, a preservative in a hair shampoo may cause a rash on the neck, a preservative in a textile may result in dermatitis where the clothing touches the skin, and one in a cream results in dermatitis wherever it has been applied.

The affected skin may become red, swollen, and blistered (acute dermatitis) or dry, thickened, and intensely itchy (chronic dermatitis). The dermatitis may occur intermittently or continuously depending on the timing of exposure. It may be difficult to distinguish contact allergic dermatitis to preservatives from irritant contact dermatitis (e.g., wet work) or constitutional dermatitis (e.g., atopic dermatitis).

Preservative allergy often presents as hand dermatitis, including occupational dermatitis – for example, in hairdressers, who use many different products containing preservatives.

Sensitization to MI, iodopropynyl butylcarbamate (IPBC), and quaternium-15 is associated more often with occupational dermatitis, whereas sensitization to imidazolidinyl urea and diazolidinyl urea is associated with face dermatitis, indicating cosmetic exposure (Schnuch et al. 2011).

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Cross-References

- Allergic Contact Dermatitis
- Hairdressers' Occupational Skin Disease
- Methyldibromo Glutaronitrile, Contact Allergy to
- Methylisothiazolinone Allergy

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Protein Contact Dermatitis

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Synonyms

Immediate contact skin reactions; Syndrome contact urticaria

Definition

The protein contact dermatitis (PCD) is an adverse immediate cutaneous reaction that occurs after the contact with certain substances.

Introduction

The protein contact dermatitis (PCD) is an entity characterized by the immediate skin development of itchy flares and dermatitis with erythema and vesicles after the contact with various substances, specially proteins or chemicals.

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Protein contact dermatitis may be caused by both nonimmunologic (irritant) and immunologic (allergic) mechanisms.

It differs from contact urticaria (CU) in that CU refers to a wheal and flare reaction following external contact with a substance that clears completely within minutes or hours without signs.

Historical Background

In 1976, Hjorth and Roed-Petersen defined this term as characterizing an immediate dermatitis induced after contact with proteins in food caterers suffering an exacerbation of itch at few minutes after contact with meat, vegetables, or fish, followed by erythema and vesicles of the hands and forearms (Hjorth and Roed-Petersen 1976).

In 1983, Veien and colleagues further characterized protein contact dermatitis (Veien et al. 1983). They defined specific criteria, including:

(1) A chronic recurrent dermatitis caused by contact with proteinaceous material
(2) An acute urticarial or vesicular eruption occurring minutes after contact with the causative protein
(3) Immediate testing results that are usually positive
(4) Patch test results that are often negative

Actually PCD is included in the called contact urticaria syndrome or immediate contact skin reaction (von Krogh and Maibach 1981), a term that encompasses nonimmunologic, immunologic, and uncertain contact urticaria, first described by Fisher in 1973.

Epidemiology

The incidence of contact urticaria syndrome (CUS) is not known.

Because PCD is relatively rare, there have been no formal epidemiologic studies. Anecdotally, risk factors for the development of protein contact dermatitis include atopy, chronic irritant dermatitis, and an occupation or hobby involving exposure to protein allergens. Approximately 50 % of cases are associated with atopy. The reasons for this are unclear.

Information from case series indicates that protein contact dermatitis is primarily seen in chefs, veterinarians, dairy workers, and workers in other occupations in which there is significant protein exposure.

Clinical Presentation

Protein contact dermatitis describes a distinct type of chronic recurrent dermatitis that differs from the wheal and flare reaction of contact urticaria. The dermatitis usually affects the hands and forearms, and these areas are typically diffusely involved. Sometimes, only the fingertips are affected. An urticarial or vesicular exacerbation can be noted a few minutes after contact with the causal protein on previously damaged skin. Other and less common sites include facial areas. Among food handlers, chronic paronychia is a not uncommon presentation, with the proximal nail fold demonstrating severe swelling and itching.

Allergens

The proteins that induce PCD are traditionally classified into four groups. These include fruits, vegetables, spices, and plants (group 1), animal proteins (group 2), grains (group 3), and enzymes (group 4) (Table 1).

PCD from vegetables is common in caterers, gardeners, and kitchen workers who have dermatitis normally limited to the hands. Only in atopic individuals we can observe systemic symptoms.

Animal protein dermatitis is most observed in fisherman, butchers, veterinarians, farmers, etc. in contact with animal guts or some fluids.

PCD associated to enzymes is most common among pharmaceutical industry workers than can associate also respiratory symptoms.

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Protein Contact Dermatitis, Table 1 Agents responsible for immediate contact reactions

Fruits, vegetables, spices, and plants	Animal proteins
Almond	Blood (pig, cow, lamb)
Apple	Amphibian serum
Asparagus	Cheese
Banana	Egg yolk
Bean	Epithelium/dander (cow, pork)
Chamomile	Fish
Caraway	Gut (pig)
Carrot	Liver (chicken)
Castor bean	Meat (beef, pork, chicken, horse, lamb)
Cauliflower	Mesenteric fat
Celery	Milk (cow's), milk products
Chicory	Saliva (cow)
Chrysanthemum	Skin (chicken, turkey)
Coriander	Worms (*Nereis diversicolor*)
Cornstarch	
Cress	
Cucumber	
Curcumin	
Curry	
Cynodon	
Dill	**Grains**
Eggplant	
Endive	Barley
Fig	Rye
Garlic	Wheat
Hazelnut	Oat flour
Horseradish	
Kiwifruit	
Lemon	
Melon	
Mugwort	
Mushroom	
Onion	**Enzymes**
Orange	
Paprika	α-Amylase
Parsley	
Parsnip	
Peach	
Peanut	
Pear	
Pineapple	
Potato	
Shiitake	
Soy	
Tomato	

Pathogenesis

The pathogenesis is not entirely understood, but all such causes of reduced stratum corneum barrier integrity may indeed facilitate high molecular weight proteins to penetrate into the skin and produce protein contact dermatitis.

The histological results of biopsies may resemble those of allergic contact dermatitis or urticaria. It is possible that first is a type I (immediate hypersensitivity) reaction with superimposed contact dermatitis (allergic or irritant).

Also it is possible that the allergens induce a combined type IV and type I reaction. That is supported by the fact that most cases of PCD arise after chronic skin irritation period.

Other possibility suggests that it involves IgE-presenting Langerhans cells similar to what occurs in atopic dermatitis.

In Table 2, there is a comparison of the allergic and protein contact dermatitis (Table 2).

Diagnosis

To diagnose protein contact dermatitis, the following tests can be used:

1. Open application test: placing the food on intact skin and in damage skin.
2. Prick test: One drop of diluted test allergen, saline serum as negative control and histamine as positive control are putting and later piercing in volar aspect of the forearm. A lecture is needed after 15–20 min, and a positive reaction is a wheal of at least half the size of histamine control. Also it is possible to realize prick-prick test, piercing the fresh product and later piercing the skin with the same needle.
3. Scratch test: Drops of commercial food tests are applied to the forearms, and needles are used to scratch the skin. With natural foods, the test begins with the scratch of the skin and later the food is applied in this area. The lecture of the test is after 30 min.
4. Patch tests: They are often negative, but some authors consider them as falsely negative,

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Protein Contact Dermatitis, Table 2 Differences between allergic and protein contact dermatitis

Allergic contact dermatitis	Protein contact dermatitis
Eczematous	Eczematous, sometimes urticarial
Hypersensitivity, type IV	
Allergens, low molecular weight	Allergens, high molecular weight
Spongiotic dermatitis with lymphocyte exocytosis and perivascular lymphocytic infiltrate	Perivascular lymphocytic infiltrate with eosinophils; espongiosis with lymphocyte exocytosis
Patch test positive	Patch test negative
Prick test negative	Prick test positive
RAST negative	RAST positive (sometimes)

and they may become positive if the allergens are occluded for longer periods or be more concentrated. Therefore, stripping of the skin previously has been recommended. Standard series are often negative because of chronic skin irritation, but patch testing should be done to exclude allergic contact dermatitis.

5. In vitro tests (radioallergosorbent test (RAST)): This test measures the amount of circulating antibodies present in serum incubated with the allergen. A negative result does not rule out the diagnosis of PCD. Also many of the protein allergens have not been identified yet.

When we have a suspicion of systemic allergy (serious extracutaneous symptoms), tests should be carried out with the necessary precautions.

Treatment

Avoidance of the allergen implicated is the first objective. However, when this is not possible, the-use of high-potency corticosteroids may be useful.

Topical tacrolimus ointment is reported to have been used successfully also in these cases.

Conclusion

Protein contact dermatitis is now recognized as being distinct from contact urticaria and allergic contact dermatitis. It most often presents as a chronic hand dermatitis that gives positive results in open application tests and prick tests and negative results in patch tests.

Common allergens include raw meat, fish, vegetables, plants, and spices. Butchers, chefs, fishermen, and veterinarians are the worker most often affected. A history of atopy is observed in about 50 % of affected individuals. Respiratory symptoms and rhinoconjunctivitis are more common in patients with protein contact dermatitis from grains or enzymes.

The pathogenesis of protein contact dermatitis is unclear, but it may be a combined type I and IV hypersensitivity reaction or perhaps be due to IgE-bearing Langerhans' cells, similar to what is observed in atopic dermatitis. Further immunologic studies will provide greater insight into the pathogenesis of this condition.

Extensive studies on the incidence and follow-up of protein allergy especially in workers resulted in guidelines to reduce its incidence in high-risk occupational population.

Cross-References

- ▶ Allergic Contact Dermatitis
- ▶ Atopic Dermatitis
- ▶ Contact Urticaria and Protein Contact Dermatitis (to Asparagus, Cow's Hair, Seafood, Etc.)
- ▶ Diagnostic Components: Allergen for In Vivo (Skin Testing, Immunotherapy) and In Vitro (Serology) IgE Antibody Testing
- ▶ Food Allergies, Diagnostic Testing

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Pulmonary Function Testing

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Synonyms

PFTs

Definition

Pulmonary function testing is comprised of three different components, each of which adds valuable information to the assessment of a patient with respiratory complaints: spirometry, which measures lung function; lung volumes, which assess various volumes during inspiration and expiration; and diffusion capacity, which is a measure of gas exchange.

Introduction

Pulmonary function testing is important in the assessment of patients presenting with respiratory complaints. It aids in the diagnosis of pulmonary conditions and often helps distinguish between various illnesses that can present quite similarly. Pulmonary function assessments can be used to determine whether a patient is safe to undergo surgery or bronchial challenge testing. In addition, pulmonary function testing can be used to assess the respiratory status of a given individual over time. For example, if a patient with asthma is complaining of a marked increase in his shortness of breath from baseline, a decrease in lung function might indicate the need for an escalation in controller therapy or for a burst of systemic steroids. Alternatively, a stable lung function in this same patient might indicate the need to look elsewhere for the cause of this patient's increasing shortness of breath.

Pulmonary function testing is comprised of three different components, each of which adds valuable information to the assessment of a patient with respiratory complaints: spirometry, lung volumes, and diffusion capacity.

Spirometry

Spirometry assesses lung function by measuring both the volume of breath that a patient can exhale and inhale and the time that it takes the patient to do this. Values obtained during spirometry are visually depicted in the flow-volume loop (Fig. 1).

In the assessment of lung diseases, one of the most important measurements obtained during spirometry is the forced vital capacity (FVC), which is the volume of air (in liters) that can be exhaled with maximal expiratory effort starting at maximal inhalation. Another important measure is the forced exhaled volume in 1 s (FEV1), which is the volume of air (in liters) exhaled with maximal expiratory effort in the first second. When reporting these values, it is most helpful to report the absolute value in liters as well as the "percent predicted." Predicted values are based on population norms and take into account a patient's age, height, and gender, since these are the factors that have been shown to affect spirometric measures. In particular, lung function decreases with increased age, shorter height, and female gender (Hegewald and Crapo 2010). There are also

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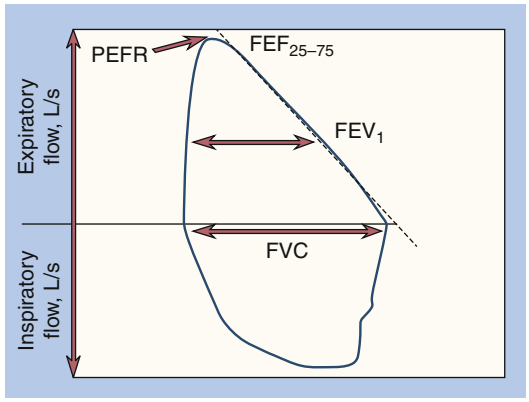

Pulmonary Function Testing, Fig. 1 Flow-volume loop with important measurements labeled (Borrowed, with permission, from Bronchial Asthma 2012, pp. 35–56. The use of the pulmonary function laboratory in diagnosing asthma Michael Schivo MD, MAS, Amir A. Zeki MD, MAS, Nicholas J. Kenyon MD, MAS, Timothy E. Albertson MD, MPH, Ph.D.)

correction factors for certain ethnic groups, such as people of African and Asian ancestry, who tend to have a lower lung function in general. A factor of −12 % is applied to the predicted values (Pellegrino et al. 2005). Predicted values for other ethnic groups may also need adjustment, but correction factors have not been delineated for every ethnicity.

Both obstructive and restrictive lung diseases are characterized by a reduction in FEV1. The degree of reduction helps define severity of disease. An FEV1 that is <60 % of predicted values indicates a severe degree of obstruction or restriction, depending on the remainder of the patient's spirometry. An FEV1 between 60 % and 69 % of predicted values defines moderate disease, and an FEV1 >70 % but less than normal defines mild disease (Hegewald and Crapo 2010).

The PEFR, or peak expiratory flow rate, is another commonly used measure of lung function and indicates the peak flow (volume of air in liters per second) that a patient is able to attain when forcefully exhaling. Portable peak flow monitors are often used by patients with asthma to get a rough idea of lung function when they are at home. Because peak flow measurements are extremely effort dependent, though, it should be used with caution and certainly not as a sole tool for diagnosing asthma. Its main use is as a home monitoring tool that can help track lung function after changes in therapy, assist patients in determining the severity of an asthma flare so that they can implement the necessary intervention, and aid those patients who are poor perceivers of their symptoms so that they might recognize a decrease in lung function earlier and potentially avoid a severe exacerbation of their asthma. When using peak flow monitors for home monitoring, an individual must first establish his or her personal best by measuring midday peak flow measurements every day for a few weeks as well as post-bronchodilator peak flows. This measurement can be used in developing a patient's home action plan, which can help some patients with home management of their asthma. In the case of therapy changes or poor perceivers of symptoms, daily tracking of peak flow measurements should occur first thing in the morning, and patients should record the best of three measurements. During a flare, patients should check their peak flow both before and after bronchodilator administration, which will give an indication as to the severity of the flare.

In Fig. 1, FEF stands for forced expiratory flow and is a measure of the flow of air at a specific point during exhalation. Similarly, FIF stands for forced inspiratory flow and is a measure of the flow of air at a specific point during inhalation. For example, the FEF25 % is a measure of the flow of air at 25 % of FVC. Intervals are denoted as ranges of percentages, with the most commonly used interval being FEF25–75 %, which is the mean of the flows between 25 % and 75 % of FVC. This measure is used by some clinicians as a way of assessing the smaller airways, although this is an area of great debate given the variability of this measure. Since the FEF 25–75 % varies from one effort to the next in a given patient, it can often overestimate or underestimate the degree of obstruction and should not be used as the sole measure when diagnosing asthma or evaluating a patient with asthma (Pellegrino et al. 2005).

One crucial factor in the interpretation of spirometry is ensuring that the technique is appropriate, which involves three factors: a back

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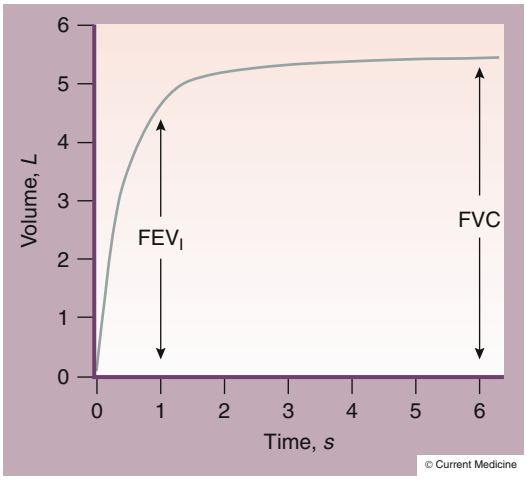
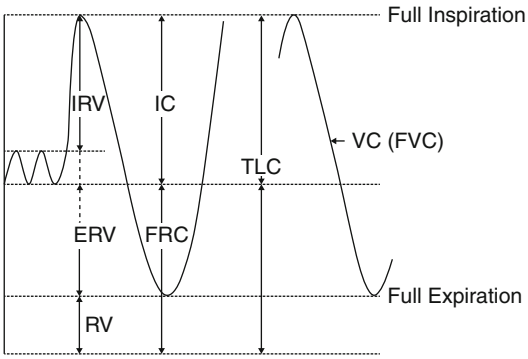


Pulmonary Function Testing, Fig. 2 Volume-time curve that is smooth, plateaus, and lasts at least 6 s (Borrowed, with permission, from Spirometry in diagnosis of COPD Source: Atlas of chronic obstructive pulmonary disorder, vol. 1, Chapter 4 ISBN: 978-1-57340-294-1 Published: 2009-01-08 Authors: Hegewald, Matthew; Crapo, Robert; Jensen, Robert)



Pulmonary Function Testing, Fig. 3 Lung volumes that can be measured and/or calculated through body plethysmography (Borrowed, with permission, from Bronchial Asthma 2012, pp. 35–56. The use of the pulmonary function laboratory in diagnosing asthma Michael Schivo MD, MAS, Amir A. Zeki MD, MAS, Nicholas J. Kenyon MD, MAS, Timothy E. Albertson MD, MPH, Ph.D.)

extrapolation of less than 5, a reproducibility between efforts, and an exhalation time of 6 or more seconds. Back extrapolation is a way of ensuring an adequate peak at initial exhalation (the PEFR in Fig. 1). If this peak is not attained, back extrapolation increases. An effort that has a back extrapolation of greater than 5 is thought to be inadequate and should be discarded and repeated. Reproducibility between efforts is the second criterion for spirometry to be deemed adequate. Three consistent trials must be performed, with consistency defined by FEV1 measurements that are within 150 mL of each other and FVC measurements that meet this same requirement. The third criterion for acceptability is an exhalation time of 6 s or greater, as shown in Fig. 2. To ensure appropriate duration, each flow-volume curve should be accompanied by a volume-time curve (Fig. 2). This curve should be smooth, reach a plateau, and last longer than 6 s for all three efforts.

Lung Volumes

In order to measure lung volumes and capacities, one must perform body plethysmography. A "capacity" is defined as the sum of two or more volumes. As shown in Fig. 3, there are four volumes and four capacities that are generally measured or calculated.

Tidal volume (VT) is the volume of air that comes in and out of the lungs during relaxed breathing. Functional residual capacity (FRC) is the amount of air left in the lungs after relaxed exhalation. It is the sum of expiratory reserve volume (ERV), which is the extra air one can exhale during maximal exhalation as opposed to relaxed exhalation, and residual volume (RV), which is the amount of air left in the lungs after maximal exhalation. Vital capacity (VC) is the total amount of air that one can exhale after maximal inhalation. Total lung capacity (TLC), which is the total amount of air in the lungs after maximal inhalation, is therefore the sum of VC and RV. Inspiratory reserve volume (IRV) is the difference between maximal inhalation and relaxed inhalation. Inspiratory capacity (IC) is the sum of VT and IRV. Lung volumes, in particular FRC and RV, are often elevated in patients with obstructive lung disease, such as asthma. Conversely, volumes will generally be decreased in restrictive lung diseases. Lung volume measurement is therefore an important adjunct in understanding and differentiating pulmonary diseases.

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Pulmonary Function Testing, Table 1 Various pulmonary conditions associated with reduced, normal, or elevated DLCO

DLCO reduced	DLCO normal	DLCO elevated
Anemia	Asthma (or high)	Pulmonary hemorrhage syndromes[b]
Interstitial lung disease[a]	COPD without emphysema	Obesity
COPD with emphysema		Polycythemia
Neuromuscular disease		Intracardiac shunts
Chest wall abnormalities		Asthma (or normal)

Data taken from Hegewald and Crapo (2010)
[a]Examples of interstitial lung disease include idiopathic pulmonary fibrosis, sarcoidosis, and drug-induced pulmonary toxicity from agents such as amiodarone or bleomycin
[b]Pulmonary hemorrhage syndromes include Wegener's granulomatosis, Goodpasture's syndrome, and idiopathic pulmonary hemosiderosis

Diffusion Capacity

Diffusion capacity of carbon monoxide (CO), abbreviated DLCO, is a measure of CO diffusion across the alveolar-capillary membrane and therefore a way of looking at gas delivery to the blood. In many areas outside of North America, DLCO is known as transfer factor or TLCO (Hegewald and Crapo 2010). When CO enters the plasma, it dissolves and binds to hemoglobin with an affinity that is over 200 times that of O_2, so it is used preferentially in this test (Chu and Han 2008). DLCO is measured by having a patient exhale to RV and then inhale to TLC with air from a chamber containing a mixture of CO and helium. The patient will then hold his/her breath for 10 s and breathe into another chamber without CO. The gas collected in the new chamber is analyzed for CO content, which is then compared to the CO content of the initial chamber to determine CO diffusion. DLCO is equal to VCO divided by PaCO or the volume of CO divided by the alveolar concentration of CO. DLCO is generally adjusted for gender, age, and hemoglobin level. Factors that affect DLCO are smoking, altitude, amount of hemoglobin, and factors related to the capillary, including surface area and thickness of the membrane and capillary blood flow. Rapid diffusion of CO is dependent on the amount of hemoglobin in red blood cells, so conditions of low hemoglobin will decrease DLCO, and the converse is true as well (Hegewald and Crapo 2010). Table 1 lists various conditions that will result in either an elevated, normal, or reduced DLCO, sometimes by altering one of these factors.

Obstructive Versus Restrictive Lung Disease

One important use for pulmonary function testing is in distinguishing obstructive from restrictive lung diseases in patients presenting with respiratory complaints. This distinction can be made by comparing lung volumes and capacities, as shown in Table 2.

Of particular importance when comparing obstructive and restrictive lung diseases is the ratio of FEV1 to FVC (FEV1/FVC) becomes an important measure. Patients with obstructive lung disease will have a disproportionate reduction in their FEV1 compared with their FVC. This observation is logical since an obstruction to airflow can be more easily overcome when time is given for a patient to empty his or her lungs fully, as represented in the FVC measurement, rather than when he or she is given just 1 s to do so, as represented in the FEV1 measurement. The disproportionate reduction in FEV1 seen in obstructive lung disease yields an FEV1/FVC ratio that is classically less than 70 %, although this measure is age dependent. Younger people without lung disease should have higher FEV1/FVC ratios, often greater than 80 % and 90 % in young adults and children, respectively. In restrictive lung disease, on the other hand, the factor that is impeding exhalation is often anatomic in nature, such as obesity or chest wall deformities, or one that

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Pulmonary Function Testing, Table 2 Differences in lung volumes and capacities between obstructive and restrictive lung diseases

	Obstructive lung disease	Restrictive lung disease
VC	↔	↓
FEV1	↓	↓
FVC	↓	↓
FEV1/FVC	↓	↔
FRC	↑	↓
RV	↑	↓
TLC	↑	↓

Data taken from Hegewald and Crapo (2010)

affects lung compliance, such as fibrosis of the lung. These abnormalities cannot be overcome with time alone, so the FVC is often reduced to the same degree as the FEV1, yielding a normal FEV1/FVC ratio. In many cases of restriction, the FEV1 is actually disproportionately elevated compared with FVC, although both are decreased compared to normal, and this yields an elevated FEV1/FVC ratio (Johns and Crockett 2008). When a pattern of restriction is noted on spirometry (i.e., reduced FEV1 and FVC with a normal or elevated FEV1/FVC ratio), it is important to obtain lung volumes, as discussed above, since restrictive lung disease is defined by low lung volumes in addition to this spirometric pattern.

Cross-References

▶ Testing: DLCO

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R

Role of IgE in Disease

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Synonyms

IgE immunoglobulin E

Definition

Role of IgE in disease: the way how variations in allergen-specific immunoglobulin E levels correlate with the manifestation and expression of IgE-mediated symptoms or diseases.

Historical Background

Originally evolved as an important component of adaptive immune responses to helminthic parasites, immunoglobulin E (Bonnelykke et al. 2008) plays a major role in triggering allergic reactions. It has been coined "immediate hypersensitivity" due to the speed of the immune reaction and the sensitivity of the IgE system. In comparison with other types of immune reactions, IgE-mediated reactions have a very rapid onset and often include itching, edema, coughing, lacrimation, bronchoconstriction, mucous secretion, vomiting, and diarrhea. Although these types of reactions are typical of allergic disease, they may also be useful in excluding parasites from the body. The abundance of IgE-secreting B cells in the skin, lungs, and gut – the main portals of entry for parasites – also suggests a connection between IgE and protection from parasites (Burton and Oettgen 2011).

Even though IgE may have developed to protect against parasites, IgE has become most closely identified with allergic disease. Whether parasitic infections protect from allergic diseases is still under debate (Feary et al. 2011). IgE levels in blood are elevated in atopic diseases such as bronchial asthma, food allergy, atopic dermatitis, allergic rhino-conjunctivitis but also in case of immune-dysregulation such as hyper-IgE syndrome, Wiskott-Aldrich syndrome, lymphomas, and finally in parasitic infections such as *Schistosoma mansoni*, *Trichinella spiralis*, *Fasciola hepatica*. It is difficult to delineate the role of IgE in the context of other diseases since it is complicated by the difficulty in learning whether changes in IgE are directly linked to disease pathogenesis or whether changes in IgE are epiphenomena resulting from other changes within the immune system.

IgE is represented in a very low amount in serum (50 ng/ml; 100.000 times less than IgG). The half-life in serum is 1–2 days, whereas in

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tissues, it may last for several weeks to months when bound to the high affinity IgE receptor on mast cells. IgE was the last of the immunoglobulins to be discovered. Initially, the component that was capable of mediating anaphylactic reactions was called "reagin," but since it did not fix complement and failed to form precipitin lines with antigens in agar diffusion reactions, it was not believed to belong to the group of immunoglobulins. Prausnitz and Küstner demonstrated the transfer of immediate hypersensitivity via transfer of sera into the skin of nonallergic individuals (Stanworth et al. 1967). The name IgE was dually described by Ishizaka et al. and Johansson et al. in 1967 (Ishizaka et al. 1966; Johansson and Bennich 1967).

Normal Serum IgE Concentrations

Serum IgE concentrations are highly variable. The high upper limits of normal and broad overlap between IgE concentrations in atopic and nonatopic people reduce the diagnostic sensitivity of total serum IgE concentrations as a screening test for allergy (Lindberg and Arroyave 1986).

Total IgE in Cord Blood

IgE does not cross the placenta; thus, cord blood IgE might relate to fetal production or cross-contamination with maternal blood. Nutritive and inhalant allergens readily cross the placenta barrier in atopic and nonatopic mothers (Szepfalusi et al. 2006). Recent studies suggest that maternal specific and total IgE closely correlate with cord blood IgE levels (Bonnelykke et al. 2008). A number of publications evaluated the predictive value of cord blood IgE concentrations for childhood allergic disease. Although initially studies suggested positive associations, more recent data suggest that cord blood IgE is of limited prognostic value (Ruiz et al. 1991; Halonen et al. 1992).

IgE in Allergic Disease

The best known function of IgE is the triggering of immediate hypersensitivity reaction. Upon exposure to the offending allergen, symptoms of allergy are induced within a few minutes after exposure. Depending on the organ of sensitization and organ of allergen encounter, this reaction can be both of local and systemic nature. Reactions include urticaria and angioedema in the skin, bronchial obstruction and sneezing, runny and blocking nose in the lower and upper airways, food-induced gastrointestinal symptoms (diarrhea, vomiting, cramping), and systemic anaphylactic reactions to insect venoms, foods, and drugs. Cross-linking of IgE with antigen triggers mast cell granule release, which contain preformed mediators and induce de novo synthesis of lipid mediators, cytokines, and chemokines. Thus, an immediate reaction is followed by a late phase reaction after 6–8 h. Again, the symptoms of airway obstruction, cutaneous swelling, gastrointestinal distress, and anaphylaxis may develop.

The natural course of IgE-mediated allergies is characterized by a genetically mediated propensity to develop IgE antibodies to nutritive and inhalant allergens. This phase is not accompanied by clinical symptoms, but may evolve to the development of clinical signs of allergy within a time frame of weeks to months. The appearance of atopic diseases is linked to a chronicity named "atopic march." Initially, food allergies, anaphylaxis to foods, and atopic dermatitis appear. Thereafter, allergic rhinitis and bronchial asthma come later, and insect venom and drug-related anaphylaxis appear at any time.

Clinical Value of Allergen-Specific IgE

The clinical value of knowing the mass units of allergen-specific IgE is not defined in detail. Some authors have reported a moderate correlation between grass pollen-specific IgE levels and symptoms during the grass pollen season. Other reports could not find any consistent correlations. Several factors influence the magnitude of total and allergen-specific IgE: person's age, degree and duration of the most recent allergen exposure, the degree and duration of exposure to

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Role of IgE in Disease, Table 1 Pros and cons of skin prick tests versus allergen-specific IgE in vitro assays

Immunoassays	Skin test
Lack of risk for allergic reaction	Greater sensitivity
Results not affected by drugs	Wider selection of allergens
Greater patient convenience	Prick-to-prick test with native allergens
Skin condition unaffected	Immediate available results
Low blood volume sufficient (chip technology)	Less time and reagent expense per test

cross-reactive allergens, and immunotherapy. Specific IgE levels are typically highest in school-age children and young adults, but may occur at any age. In contrast, sera from children with atopic dermatitis often have very high total concentrations of specific IgE, which may produce nonspecific binding and lead to clinically irrelevant false-positive results. Thus, interpretation of allergen-specific IgE values needs a certain degree of experience accounting for all influencing confounder factors. Allergen-specific IgE usually rises as a result of pollen exposure. The levels of specific IgE typically peak approximately 4 weeks after a seasonal pollen exposure and then gradually fall to a lowest value before the next pollen season. IgE levels also tend to decline during immunotherapy, but very steadily and slowly. Thus, changes in specific IgE levels do not help to monitor success of an allergen-specific immunotherapy.

Indication for Measuring Specific IgE Antibodies

Once the clinical decision, based on history, has been made to test for allergen-specific IgE, in vivo or in vitro tests (Table 1) are available and, despite overlapping features eventually display relative advantages as compared to the other (Burton and Oettgen 2011).

A confounding factor for in vitro detection of allergen-specific IgE is the presence of cross-reactive IgE antibodies. Many individuals allergic to hymenoptera or pollen have detectable IgE antibodies to foods, and 20–30 % of those with food-specific IgE antibodies do not report symptoms related to foods. New developments in the understanding of cross-reactivities have led to the detection of molecular compounds of allergenic sources. These molecules (e.g., bromelain) are now available for diagnostic purposes and help to discriminate between primary and cross-reactive sensitization (Fiocchi and Nowak-Wegrzyn 2011).

IgE in Food Allergy

Although less common than allergic rhinitis, atopic dermatitis, and asthma, the prevalence of food allergy as a genuine disease is rising, and IgE-mediated food reactions can be severe (Fig. 1a–d). The clinical observation that the presence of allergen-specific IgE can almost always be demonstrated in patients undergoing food anaphylaxis has implicated IgE antibodies as the key effectors. However, it is also clear that the presence of IgE antibodies is not sufficient to confer anaphylactic sensitivity. A considerable percentage of children with measurable levels of food-specific IgE do not have clinically relevant food allergy. On the other hand, children with established food allergy in infancy will lose their clinical reactivity and become tolerant within the next months and years. Although clinically cured, these children very often carry their IgE sensitization profile for many more years. These observations suggest that additional effector mechanisms must be in place for the full expression of IgE-mediated food allergy, at least in some patients. In mouse models, an IgE-independent, IgG-mediated, mast cell exclusive macrophage FcgRIII-bound mechanism was described. PAF was found to be released substituting for histamine to increase vascular permeability and bronchoconstriction (Finkelman 2007).

IgE in Infectious and Parasitic Disease

Serum IgE levels are measured in many infections and parasitic diseases (Table 2)

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Role of IgE in Disease, Fig. 1 Food provocation revealing clinical reactivity to minute amounts (μg) of peanut (**a**) before exposure (**b**) angioedema and respiratory distress (**c**) angioedema, facial urticaria, and respiratory distress (**d**) urticaria

(Obeng et al. 2008). The changes noted in some infectious appears to be the result of IgE antibodies specific for the infectious agent, whereas in other diseases, changes in IgE appear to be nonspecific (Ruiz et al. 1991).

Increased total IgE levels occur during metazoan parasitic infections. Association between parasitic tissue invasion and height of IgE levels has been described. Increased IgE levels are based on both parasite-specific and nonspecific IgE production. One mechanism proposed to explain the increase in total IgE levels is the secretion by parasites of factors that stimulate interleukin 4 production, which in turn stimulates IgE production by plasma cells. After successful treatment of parasitic infections, total IgE levels seem to fall.

IgE in Neoplastic Disease and Bone Marrow Transplantation

Elevated total IgE has been described for many different neoplastic diseases, such as Hodgkins disease, IgE myeloma, bronchial carcinoma, and breast cancer (Samoszuk and Ramzi 1993). Again, successful treatment of neoplastic diseases has been associated with reduced total IgE levels. The current understanding of the clinical importance of IgE in most of these diseases is limited. Alterations in immune function, such as decrease in regulatory function and/or uncontrolled polyclonal B cell activation, are possible explanations.

After bone marrow transplantation, increases in serum total IgE levels have been observed in

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Role of IgE in Disease, Table 2 Nonallergic diseases associated with increased total serum IgE levels; according to (Smith and Ownby 2009)

Parasitic diseases	Ascariasis
	Visceral larva migrans
	Fascioliasis
	Schistosomiasis
	Trichinosis
	Filariasis
	Strongyloidiasis
	Malaria
	Echinococcosis
	Onchocerciasis
	Hookworm
Infections	Allergic bronchopulmonary aspergillosis
	Candidiasis
	Coccidioidomycosis
	Leprosy
	EBV
	CMV
	HIV
	Pertussis
	Measles
Cutaneous diseases	Bullous pemphigoid
	Erythema nodosum (*Streptococcus*)
	Chronic acral dermatitis
Neoplastic diseases	Hodgkin´s disease
	IgE myeloma
	Bronchial carcinoma
	Breast cancer
Immunodeficiency diseases	Wiskott-Aldrich syndrome
	Hyper-IgE syndrome
	DiGeorge syndrome
	Nezelof syndrome
	Selective IgA deficiency
Other diseases	Liver diseases
	Cystic fibrosis
	Kawasaki disease
	Primary pulmonary hemosiderosis
	Guillain-Barré syndrome
	Rheumatoid arthritis
	Bone marrow transplantation
	Cigarette smoking
	Alcoholism

a great range (up to many thousand fold). Graft-versus-host disease was suspected, but IgE increase occurs also without GVHD (Ringden et al. 1983). Myeloablative treatment was also suspected, but bone marrow transplantation also led to IgE increase without myeloablation (Table 2).

IgE and Renal Disease

Increased total IgE levels have been described in patients with nephrotic syndrome associated with different forms of glomerulonephritis (Miyazaki et al. 2011). High IgE levels were particularly associated with a low response rate to steroids. With adequate therapy, total IgE concentrations decline. The reason for the association is currently unexplained (Table 2).

Cross-References

- ▶ Genetic Regulation of IgE
- ▶ Hyper-IgE Syndrome
- ▶ IgE Testing

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Role of Mast Cells in Diseases

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Synonyms

Autoimmune diseases; Multiple sclerosis (MS); Respiratory allergies; Rheumatoid arthritis (RA); Tumor immunity

Definition

Mast cells are cells of innate immunity that play a central role in allergic diseases such as rhinitis, asthma, urticaria, and anaphylaxis. These cells also have a detrimental effect on the development and progression of autoimmune diseases including multiple sclerosis, rheumatoid arthritis, pemphigus, SLE, and others. In these diseases, mast cells are increased at sites of organ damage and are presumably activated via their IgE- and IgG-binding receptors and Toll-like receptors. Mediators released by mast cells influence the activity of T cells, B cells, neutrophils, and other effector cells of autoimmunity. Mast cells are also associated with several types of cancer where they represent on the main cell type infiltrating neoplastic tissue. There is clear evidence that mast cells contribute to cancer growth by modifying the tumor microenvironment where they induce immunosuppression, promote angiogenesis, and favor the release of metastatic cells.

Introduction

Mast cells are widely distributed within organs and tissues and are particularly abundant at large surface areas in contact with the external environment, that is, the skin, respiratory tract, and gastrointestinal tract. This strategic location explains the main function of mast cells as cells of innate immunity and as homeostatic regulators of immune and inflammatory responses. The key role of mast cells in orchestrating defense responses to external or internal aggressions also helps to define their participation to a variety of diseases including allergic, inflammatory, autoimmune, and neoplastic disorders. In the last few decades, several aspects of mast cells' role in diseases have been elucidated primarily by experimental studies in animals, which have been later confirmed in human studies. In general, mast cells can contribute to the initial development and to progression of certain diseases by secreting soluble mediators that trigger and sustain inflammation directly or influence functions of other immune or inflammatory

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cells. However, direct cell-cell interactions of mast cells with various subsets of T cells appear to be important for dysregulation of immune responses. In addition, mast cells participate in the development of tissue damage and remodeling, which often result in long-term organ damage associated with asthma and autoimmune diseases.

As cells of innate immunity, mast cells play a major role in the defense against viral and bacterial infections. In this setting, mast cells support the activity of several effector cells including neutrophils, eosinophils, and macrophages primarily by releasing TNFα. The role of mast cells in infectious diseases should be considered a physiological response and thus it will not be discussed here. This entry will rather focus on the pathophysiology of altered mast cell responses in allergic and autoimmune disorders and cancer, conditions in which these cells are thought to contribute significantly to disease progression.

Mast Cells in Allergic Diseases

Allergic diseases are the most frequent immunological disorder in the general population and their prevalence is continuously increased in the last decades. The primary role of mast cells and their mediators in respiratory and skin allergies has been clearly established since their discovery more than a century ago. Mast cells are pivotal in all phases of the development of allergic rhinitis and asthma, including sensitization to allergens, regulation of the IgE response, occurrence of clinical manifestations, and long-term complications and comorbidities. Early studies demonstrated that mast cells are regulators of epithelial cell functions in both the respiratory and gastrointestinal tracts whereby they modulate mucosal permeability and antigen entry. Furthermore, mast cells are important in the process of activation and maturation of dendritic cells by releasing histamine, prostaglandin D_2 (PGD_2), and TNFα. These mediators strongly increase the ability of dendritic cells to take up and process antigens and to migrate to regional lymph nodes for subsequent T cell activation. Other mast cell-derived mediators concur at later stages to promote recruitment of Th2 cells at sites of allergic inflammation. For example, PGD_2 produced by activated mast cells is the ligand of CRTH2 receptor highly expressed on Th2 cells and involved in their homing within peripheral tissues. Moreover, mast cells, together with basophils, are a major source of IL-4 and IL-13, the leading cytokines responsible for immunoglobulin switch toward IgE synthesis.

The number of mast cells is significantly increased in the mucosa of patients with rhinitis and asthma. These cells, which in healthy individuals are usually limited to the subepithelial space, are largely expanded in the bronchi of asthmatics where they are found within the epithelial layer and, to a larger extent, in the smooth muscle layer. Other changes in mast cell distribution and phenotype in asthmatics include a significant trend to higher numbers of chymase-positive mast cells in the proximal airway epithelium of individuals with more severe asthma (such chymase-positive intraepithelial mast cells are rarely seen in healthy individuals) and a significant trend toward lower levels of submucosal mast cells in the proximal airways, but a significantly higher ratio of chymase-positive mast cells to total mast cells, with increasing severity of asthma (Balzar et al. 2011).

Binding of allergens to specific IgE on the surface of mast cells triggers degranulation and activation of cytokine and chemokine release. Mediators derived from mast cells are responsible for the majority of signs and symptoms of allergic rhinitis and bronchial asthma. Histamine, cysteinyl leukotrienes, and platelet-activating factor (PAF) are potent bronchoconstrictors and effectively induce edema, increase mucus secretion, and play a role in the recruitment of inflammatory cells in both upper and lower airways. Earlier studies demonstrated that the levels of two mediators primarily derived from activated mast cells, histamine and PGD_2, in the bronchoalveolar lavage correlate with the severity of asthma. Morphological studies of autopsy specimens revealed evidence for higher levels of degranulation of mast cells in the airway smooth muscle of individuals with fatal asthma than in individuals without asthma or those with nonfatal

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asthma, as well as increased numbers of neutrophils and degranulated mast cells in submucosal glands (Carroll et al. 2002). By altering proximity of mast cell populations to key airway structural cells that are targets of mast-cell–derived mediators and possibly by changing the reactivity of mast cells to various stimuli, such strategic relocation of mast cells may influence the extent to which they contribute to airway functional and structural changes in asthma (Galli and Tsai 2012).

While mast cells are largely represented in the gastrointestinal tract, their exact role in food allergy is not fully understood. High levels of histamine, TNFα, IL-5, and tryptase in serum, intestinal lavage fluid, and stool samples of patients suffering from food allergy support the concept of mast cell activation in these patients (Bischoff and Crowe 2005). Impairment of intestinal barrier function is of importance in food allergy, and it has been shown that inflammation enhances intestinal mucosal permeability by mast cell-dependent mechanisms. Thus, mast cells can contribute to intestinal inflammation by facilitating influx of potential allergens and harmful microbes into the intestinal tissue (Bischoff 2009). Furthermore, it has been shown that IgE-stimulated mast cells trigger enteric nerves resulting in pain and diarrhea (Kraneveld et al. 2012). As described for the human lung, tryptase- and chymase-positive mast cells are found in the submucosa of the intestinal tract, whereas tryptase-positive mast cells are located in the mucosa (Groschwitz et al. 2009). However, not much is known about the mast cell phenotype involved in food allergic patients. Recent evidence supports the hypothesis that the tryptase- and chymase-positive mast cell population is responsible for the food allergy symptoms such as decreased barrier function and diarrhea.

Mast Cells in Autoimmune Diseases

There are many similarities in the alterations of immune response observed in allergic and autoimmune disorders. In both cases, a dysregulated immune and inflammatory reaction is generated against innocuous or self-antigens as a result of a loss of immune tolerance. The potential role of mast cells in autoimmune diseases has been investigated over the past few decades primarily by using experimental models of mast cell-deficient mice. A main mechanism by which mast cells participate in the development of autoimmune diseases is by interacting with T and B cells that are the primary effector cells of the wrong immune response against self-antigens. Mast cells can influence T and B cell responses by multiple mechanisms: first, by cell-cell signaling mediated by ligands expressed on mast cells (OX40L, CD30L, CD40L) that bind to their counterpart on T and B cells; second, by producing mediators, cytokines, and chemokines that modulate the development and functions of several T cells subsets; and, third, by acquiring a specific "regulatory" phenotype that enables them to cooperate with suppressor T cells (Walker et al. 2012).

There is strong evidence that mast cells are activated within organs that are targets in autoimmune diseases like, for example, the joints in rheumatoid arthritis, lymph nodes in systemic lupus erythematosus, brain in multiple sclerosis, etc. A main question that remains to be solved is how mast cells can be recruited and activated in these autoimmune disorders since it is likely that IgE-independent rather than IgE-dependent mechanisms are involved. Human mast cells express multiple receptors that can be potentially activated during an inflammatory and autoimmune response (Fig. 1). Among these, Toll-like receptors (TLRs) are thought to play a major role in mast cell activation in autoimmune diseases. Several TLRs are expressed on human mast cells, and they may be engaged by bacterial and viral products that potentially represent early stimuli to trigger an autoimmune response (Kulka et al. 2004). Furthermore, some of these receptors are activated by self-antigens such as DNA and RNA, and, therefore, they can sustain mast cell activation once tissue damage is induced and perpetuated by the autoimmune response. Besides receptors for IgE, human mast cells express receptors for IgG (FcγRII and FcγRIII). These receptors may be activated by immune complexes containing IgG and thus may be an additional way to promote mast cell recruitment

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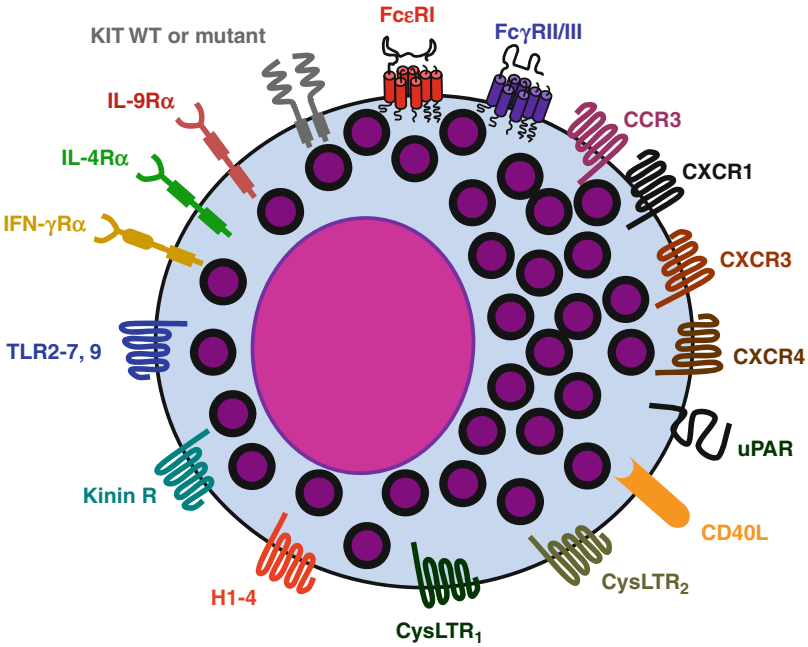

Role of Mast Cells in Diseases, Fig. 1 Functional receptors expressed on human mast cells

and activation in autoimmune disorders. The best evidence for the role of mast cells in autoimmune diseases derives from clinical and experimental studies on multiple sclerosis and rheumatoid arthritis. However, mast cells are implicated in other autoimmune diseases including type I diabetes, Guillain–Barré syndrome, Graves' ophthalmopathy, pemphigus vulgaris, systemic lupus erythematosus, and Sjogren's syndrome (Walker et al. 2012).

Mast Cells and Multiple Sclerosis (MS)

MS is a progressive demyelinating disease of the central nervous system (CNS) characterized by widespread inflammatory lesions in the brain and spinal cord associated with a T cell-dependent response against myelin antigens. The mechanisms underlying this condition have been extensively investigated in the murine model of experimental autoimmune encephalitis (EAE), a condition closely mimicking human MS. IFNγ-secreting T helper 1cells (Th1), IL-17-producing Th17 cells, and IL-9-producing Th9 cells have been implicated in EAE, although their role in MS is still unclear (Fletcher et al. 2010). An increased number of mast cells have been consistently observed at sites of inflammatory demyelination in patients with MS and rodents with EAE (Ibrahim et al. 1996). Microarray studies revealed that gene transcripts for tryptase and FcεRI are significantly increased in chronic lesions of MS (Lock et al. 2002). Levels of tryptase are elevated in the cerebrospinal fluid of patients with MS and tryptase as well as other mast cell-derived proteases have been involved in myelin degradation (Johnson et al. 1988). Interestingly, myelin has been shown to directly induce mast cell degranulation (Johnson et al. 1988). More recently, direct evidence for mast cell action in EAE came from studies utilizing mast cell-depleted mice in a model of progressive MS (Secor et al. 2000). Mast cell deficiency leads to a substantially less severe disease with reduced loss of blood/brain barrier permeability and inflammatory cell infiltration within CNS. TNFα produced by meningeal mast cells has been implicated in neutrophil recruitment in the early stage of the disease. Consistent with this hypothesis, entry of neutrophils into the meninges and the CNS parenchyma is abrogated in the absence of mast cells or mast cell-derived TNFα (Secor et al. 2000).

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Mast Cells and Rheumatoid Arthritis (RA)

RA is a chronic systemic inflammatory disease that affects primarily the joints and periarticular tissues. Mast cells are normally present in the joint of healthy individuals, but their number is greatly increased in the synovial compartment of patients with RA. A pathogenetic role for mast cells in RA was first hypothesized in the experimental model of antibody-induced arthritis (AIA) by using two distinct strains of mast cell-deficient mice (SI/SI^d and W/W^v). These strains were resistant to the development of AIA and susceptibility to arthritis was restored in W/W^v mice by mast cell engraftment (Lee et al. 2002). Mast cells produce a wide set of proinflammatory and immunoregulatory mediators and cytokines that deeply influence functions of synovial macrophages and fibroblasts. For example, it has been reported that mast cells are the main source of IL-17 in human RA synovium (Hueber et al. 2010). Activated synovial mast cells also secrete TNFα that in turn induces IL-1β production from macrophages. Mast cell-derived tryptase complexes with heparin stimulate fibroblasts to generate CXCL1, CXCL5, and CXCL8, which are crucial for recruitment and activation of neutrophils in the synovial fluid (Walker et al. 2012). In addition, tryptase-mediated activation of protease-activated receptor 2 (PAR-2) on synovial cells leads to increased vascular permeability and inflammation and promotes fibroblast hyperplasia by inhibiting Fas-mediated apoptosis of these cells (Sawamukai et al. 2010). Synovial fibroblasts were shown to produce IL-33, which directly activates mast cells to express high levels of proinflammatory cytokines (such as IL-17, IL-1β, IL-6, IL-13, GMCSF) and chemokines (MCP-1 and MIP-1α). These molecules recruit inflammatory cells including neutrophils, as well as promoting autoreactive Th17 phenotype (Walker et al. 2012).

Mast Cells and Cancer

In the last decades, the interest in research on cancer development and growth has progressively moved from the cancer cell itself to the wide spectrum of immune and inflammatory cells infiltrating the tumor. Mast cells have long been recognized as major components of the heterogeneous population of cells that can be detected inside and at the border of several human types of cancer. Mast cells are of an early infiltrating cell type prior to tumor development or at the periphery of many developing tumors, such as adenomatous polyps, skin dysplasias, malignant melanoma, breast carcinoma, and colorectal carcinoma (Liu et al. 2011). There is compelling evidence that mast cell accumulation within tumors is primarily led by stem cell factor (SCF) that is produced by several types of cancer cells. SCF binds to KIT expressed on mast cells and promotes their recruitment, differentiation, and survival within the tumor (Huang et al. 2008). In addition, SCF enhances mediator production from mast cells activated locally by various stimuli including damage-associated molecular patterns (DAMPs). These molecules are potent TLR ligands and induce downstream signal transductions and mast cell activation. Other molecules have also been identified as potential TLR ligands in tumor microenvironment, including the degraded products of extracellular matrix components and nuclear materials (Kulka et al. 2004).

Several studies confirmed that mast cells profoundly influence solid tumor microenvironment primarily by secreting mediators (histamine, cysteinyl leukotrienes, VEGFs), cytokines (IL-1β, IL-6, TNF-α), and chemokines (IL-8, CCL2, and CCL5). Overall, these mast cell products concur to establish a molecular and biochemical environment that is favorable to tumor development and progression. The tumor-promoting activity of mast cells is based on multiple mechanisms. First, several mediators secreted by mast cells, including several isoforms of VEGFs (VEGF-A, -B, -C,and -D, placental growth factor) angiopoietin-1 and -2, tryptase, and IL-8 promote angiogenesis that support cancer growth by providing de novo blood vessel formation and increasing oxygen supply to the tumor mass (Detoraki et al. 2009). Most of these mediators also induce lymphangiogenesis that favors metastatic diffusion of cancer cells (Fig. 2). A second mechanism by which mast cells support tumor growth is by inducing

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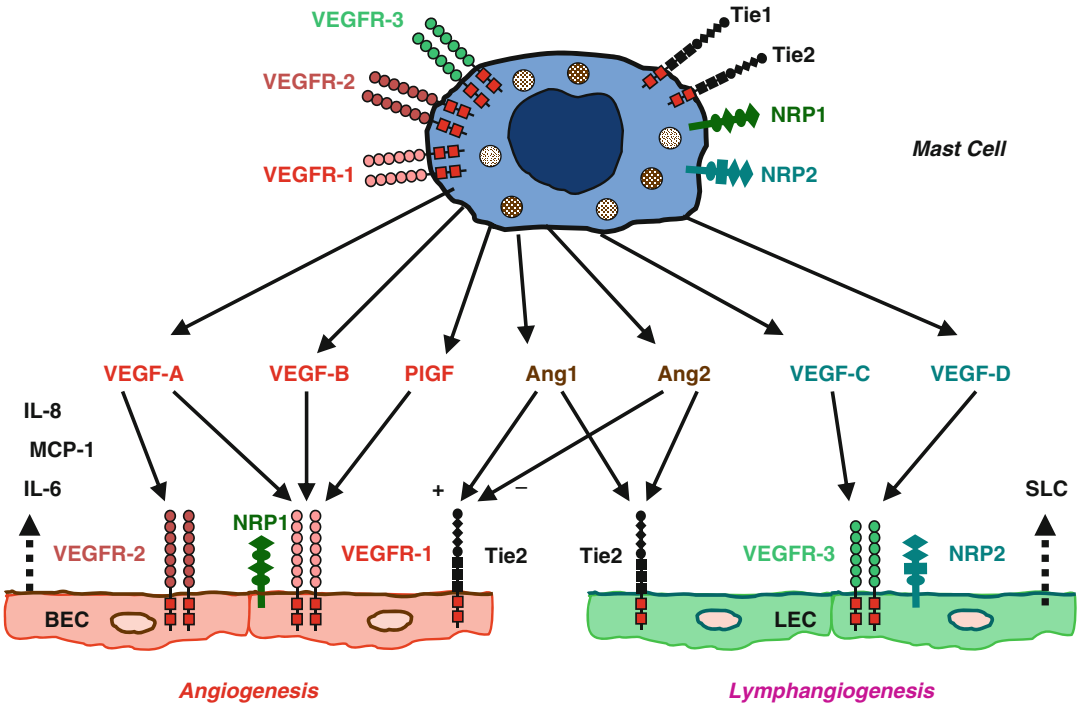

Role of Mast Cells in Diseases, Fig. 2 Proangiogenic factors produced by human mast cell and their receptors. *Ang* Angiopoietin-1 and -2, *BEC* blood vessel epithelial cell, *LEC* lymphatic vessel endothelial cell, *PlGF* placental growth factor, *Tie* receptors for angiopoietins, *NRP* neuropilin-like receptors, *VEGF* vascular endothelial growth factor, *VEGFR* VEGF receptors (Modified from Detoraki et al. 2009)

a proinflammatory environment through the release of IL-1β, TNFα, and IL-18. These mediators increase the interstitial fluid volume by plasma effusion and amplify the distance of oxygen needed to be delivered to oxygen hungry cancer cells, thus leading to hypoxia-induced metastasis. In addition, activated mast cells release proteases such as MMP9, tryptase, chymase, and cathepsin that degrade the extracellular matrix and facilitate tumor cell migration and invasion. Finally, the third, and probably most important, mechanism by which mast cells support cancer growth is by inducing a potent immunosuppressive microenvironment. The suppression of the immune response against the tumor is mainly centered on the interaction of mast cells with the tumor-associated myeloid-derived suppressor cells (MDSCs) and with Tregs. Tumor-infiltrating mast cells promote the migration and suppressor function of MDSCs by regulating the expression of CCL2 and Th2 cytokines. In fact, CCL2 and other factors recruit more MDSCs to tumor microenvironment and further exacerbate tumor inflammatory microenvironment by IL-17 secretion, leading to increased levels of CCL17 and CCL22. In turn, CCL17 and CCL22 chemoattract more Tregs to tumor site and enhance their suppressive function (Liu et al. 2011).

Given their predominant role in the remodeling of tumor microenvironment, mast cells may contribute to promote tumor initiation, progression, and metastasis. However, despite the large body of evidence in support of their protumorigenic role, many molecular and functional aspects of tumor-associated mast cells remain to be elucidated.

Cross-References

▶ Mast Cell Mediators

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Safety of Immunotherapy

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Synonyms

Allergen immunotherapy; Allergen-specific desensitization; Allergy immunotherapy; Allergy injections; Allergy shots; Hyposensitization; Immunotherapy

Background

Although the benefits of immunotherapy have been well demonstrated for the treatment of many allergic conditions such as allergic rhinitis, allergic asthma, and stinging insect allergy (Casale and Stokes 2011), the risks of adverse reactions must be considered when immunotherapy is used.

Local Reactions

Localized reactions at the site of immunotherapy injections are fairly common, with frequencies ranging from 26 % to 82 % patients and 0.7 % to 4 % of injections (Cox et al. 2011). These local reactions may involve local erythema, swelling, and itching. In one survey of 249 patients undergoing immunotherapy and who experienced local reactions, 84.7 % reported reactions smaller than the palm of the hand, and 81.9 % classified local reactions as not bothersome at all or only slightly bothersome. Ninety-six percent of these individuals who had local reactions stated they would not stop immunotherapy because of the local reactions (Coop and Tankersley 2008). In one retrospective study, local reactions were found to not be predictive of local reactions at the next injection (Calabria et al. 2009). Individual local reactions also do not appear to be predictive of subsequent systemic reactions. However, some individuals who have a large frequency of large local reactions may have an increased risk for future systemic reactions (Cox et al. 2011).

Systemic Reactions

Systemic reactions to immunotherapy involve organ-specific systems distant from the injection site and can be very serious with symptoms potentially including generalized rash/urticaria, rhinorrhea, dyspnea, wheezing, hypotension, and anaphylactic shock (Windom and Lockey 2008). Although the risk of severe systemic reactions is very low, life-threatening and fatal reactions do occur. The prevalence of severe systemic reactions after immunotherapy ranges from less than 1 % of patients receiving conventional immunotherapy to about 34 % of patients who undergo rush immunotherapy (Cox et al. 2011).

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A review of systemic reaction rates reported in studies published within the past 15 years found the rate of systemic reactions per injection with conventional immunotherapy to be approximately 0.2 % (Cox et al. 2010). Through survey data, it is estimated that the fatality rate in the United States from immunotherapy injections is about one per 2.5 million injections (Nelson 2009).

Specific Important Considerations and Precautions

Asthma: Immunotherapy for asthma should not be initiated unless an individual's asthma is stable and under control. Patients with severe or uncontrolled asthma have an increased risk for systemic reactions when receiving immunotherapy injections. Moreover, fatal and near-fatal reactions from immunotherapy injections were found to be more common in those with severe asthma. An assessment of a patient's asthma control should be performed prior to each immunotherapy injection (Cox et al. 2011).

Timing of Anaphylactic Reactions: Most serious systemic reactions from immunotherapy injections occur within 30 min after an injection. Therefore, patients should remain in the physician's office/medical facility for at least 30 min after an immunotherapy injection for continued observation (Cox et al. 2011).

Beta-Adrenergic Blocker Medication: Use of beta-adrenergic blocking agents is a risk factor for more serious and treatment-resistant anaphylaxis. Concomitant use of beta-blocker medications and immunotherapy should be carefully considered from an individual patient's risk/benefit standpoint (Cox et al. 2011).

Angiotensin-Converting Enzyme (ACE) Inhibitor Medication: A greater risk of more severe reactions from venom immunotherapy has been associated with the use of ACE inhibitors. Discontinuation of ACE inhibitors should be considered for patients receiving venom immunotherapy. If ACE inhibitor therapy is required and no alternative therapy is available, then immunotherapy should be carefully considered from an individual patient's risk/benefit standpoint (Cox et al. 2011).

Pregnancy: Immunotherapy can be continued but is typically not initiated in a pregnant individual. If an individual becomes pregnant during the buildup phase of immunotherapy, and the current dose of immunotherapy is subtherapeutic, then discontinuation of immunotherapy should be considered (Cox et al. 2011).

Cross-References

- ▶ Allergen Immunotherapy, Overview
- ▶ Immunotherapy for Allergic Rhinitis
- ▶ Immunotherapy for Asthma
- ▶ Immunotherapy for Hymenoptera Allergy
- ▶ Immunotherapy, Mechanisms
- ▶ Immunotherapy with Recombinant and DNA-Conjugated Allergens
- ▶ Sublingual Immunotherapy

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Sensitization and Allergy to Natural Rubber Latex

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Synonyms

Caoutchouc; Latex allergy

Definition

While additives which are required for the manufacturing process and for stabilization of rubber (like the sulfur-containing vulcanizers (mercaptobenzothiazoles, carbamates, thiurams), antioxidants (amines), and rubber pigments) may induce an allergic late-phase (type IV) sensitization and allergic contact dermatitis (Shah and Chowdhury 2011), rubber products made from natural latex contain a small amount of proteins, which can induce immediate-type (type I) sensitization and allergic immediate-type symptoms. This entry will focus on sensitization and allergy to natural rubber latex produced from the rubber tree *Hevea brasiliensis*.

Historical Background

Latex is a sap-like extract which is derived from various plants. It is usually exuded upon tissue injury and has important functions involved in wound healing and antimicrobial defense. Latex contains a complex mixture of various biochemical compounds, e.g., proteins, resins, and gums. Some components of latex (poly-cis-isoprene) qualify for raw material for rubber products. Several plants serve as latex sources, e.g., the rubber tree (*Hevea brasiliensis*), guayule (*Parthenium argentatum*), gutta-percha tree (*Palaquium*), or *Manilkara chicle*. The most important source is the rubber tree *Hevea brasiliensis*.

Initially, *Hevea brasiliensis* grew only in the Amazon rainforest in Brazil. The discovery of the vulcanization procedure in 1839 by Charles Goodyear and the local monopole on the plants caused a regional economic boom in that region. Although exporting seeds or living trees was prohibited, in 1875, British citizens finally succeeded to smuggle seeds to Kew Garden in London. After the seeds had germinated, seedlings were sent to the British colonies Ceylon and Singapore. Today, the most important producers of natural rubber latex (in the following named latex) are located in the Far East (Thailand, Indonesia, Malaysia, India, and China). In addition *Hevea brasiliensis* is also cultured in Africa (Ivory Coast, Nigeria, and Liberia) (http://en.wikipedia.org/wiki/Latex_allergy).

The first allergic, immediate-type symptoms elicited by rubber contact were observed upon exposure to dental materials and rubber-coated cables. Later, also household gloves, condoms, balloons, pacifiers, and other products containing latex were found to induce immediate-type symptoms. With increasing use of medical gloves, allergic reactions became an important medical problem mainly for health-care workers and for certain patient groups with a history of repeated surgical procedures, e.g., because of congenital malformations (spina bifida). The increasing use of medical gloves and a simultaneous change in the production process both increased the risk of immediate-type allergies. The mass production of low-priced medical gloves was associated with a shortening of washing processes and with a decreased denaturation of latex allergens by reduced ammonia. As a result, medical gloves were rich of intact latex proteins. Another important aspect contributing to the epidemic of latex allergy was the powdering of medical gloves with cornstarch instead of talcum. Latex allergens excellently bind to cornstarch powder, thereby contaminating large areas by airborne powder particles loaded with latex allergen.

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Allergens

Ultracentrifugation of the fresh rubber sap results in nine fractions of which three can most easily be discerned: rubber particle proteins, the C-serum, and the bottom fraction (B-serum). Rubber particles are water insoluble, whereas most of the C- and B-serum proteins are water soluble (Steinman and Ruden 2008). Proteins are classified into rubber particle proteins, C-serum proteins which present in the cytosol fraction, and B-serum proteins which are extra-cytosolic proteins.

More than 200 proteins have been identified in latex from *Hevea brasiliensis*, and about one quarter of them may bind to human IgE, a process which is a necessary prerequisite for the induction of immediate-type allergy. Thus far, 14 allergens of *Hevea brasiliensis* (Hev b) have been identified (http://www.allergome.org, Table 1). Some of them contain different allergenic fragments like prohevein, which yields Hev b 6.02 and 6.03. Others exist in various isoforms. Latex allergens either belong to plant defense proteins or are involved in the biosyntheses of polyisoprene and in the coagulation of rubber elongation factor. Some latex allergens have structural- or pathogenesis-related functions.

Different patient groups, i.e., patients with congenital malformations and health-care workers, exhibit a different sensitization pattern. Moreover, the sensitization pattern may vary between different regions. These observations may be explained by the finding that latex allergens are not homogenously distributed in the glove, i.e., outside or inside parts of medical gloves may present different allergens. Furthermore, the manufacturing process may change the composition of latex allergens in rubber products, thereby causing different sensitization patterns.

Some latex allergens show sequence homology to allergens from other sources (fruits, vegetables, indoor plants, or molds), thereby explaining the cross-reactivity between latex and foods. On the other hand, sensitization to latex may be primarily acquired by the exposure to non-latex allergens, suggesting that latex sensitization or allergy is a secondary phenomenon (Rihs et al. 2006).

Symptoms

Latex allergy may involve all symptoms of an IgE-mediated disease, ranging from urticaria, rhinoconjunctivitis, or asthma to anaphylactic shock. Symptoms are classified according to the severity grade in mild (only skin manifestation), moderate (mild internal symptoms), severe (anaphylactic shock), and fatal or near-fatal reactions (Ring and Meßmer 1979). Another form is the "contact urticaria syndrome" (Gimenez-Arnau et al. 2010), which, however, is not universally accepted. The first latex-associated fatal or near-fatal anaphylactic reactions were observed during surgical procedures or invasive diagnostics (e.g., barium enema examination). Today, unrecognized latex allergy is responsible for about 20 % of perioperative anaphylaxis (Mota and Turrini 2012).

Nearly all patients suffering from latex allergy complain about contact urticaria, itching, and/or erythema at the site of direct exposure (mostly to latex gloves or other latex rubber material). Some patients also develop more widespread urticaria, and systemic reactions of the respiratory tract, cardiovascular system, or visceral organs may occur upon either skin contact or allergen uptake through the surgical sites. In addition, respiratory symptoms may be elicited when powdered latex gloves are used. Other manifestations are delayed eczematous reactions due to a late-phase immediate-type reaction at the site of latex exposure (protein contact dermatitis). Finally, it has been discussed that latex allergy might result in disturbed wound healing.

Frequently, cross-reactivity between latex and certain, mainly tropical, foods (e.g., banana, chestnut, kiwi, avocado) induce anaphylactic reactions to food (Blanco et al. 1994). Another cross sensitization may be caused by the common indoor plant weeping fig (*Ficus benjamina*).

Epidemiology

The major risk factors for becoming sensitized to latex are intense exposure to latex allergens, preexisting hand eczema, and atopy (defined as

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Sensitization and Allergy to Natural Rubber Latex, Table 1 Allergens of *Hevea brasiliensis* (Hev b) (http://www.allergome.org; Yeang 2004; Steinman and Ruden 2008)

Name	Common name		Significance as allergen for	Cross-reactivity
Hev b 1	Rubber elongation factor	RPP	+++ → P[a]	
Hev b 2	Glucanase	B	++ → HCW[b]	Allergen possibly responsible for cross-reactivity with food allergens → "Latex-fruit syndrome"
Hev b 3	Small rubber particle protein	RPP	+++ → P[a]	
Hev b 4	Component of microhelix complex, lecithinase homologue	B	?	
Hev b 5	Hev b 5-like	C	+++ → HCW[b] +++ → P[a]	Re
Hev b 6.01	Prohevein	B	+++ → HCW[b] and P[a]	High for Hev b 6.01 and 6.02 (banana, kiwi, avocado)
Hev b 6.02	N-terminal hevein	B	+++ → HCW[b] and P[a]	
Hev b 6.03	C-terminal hevein		+++ → HCW[b] and P[a]	
Hev b 7.01	Patatin (esterase)	B	?	Structural homology to proteins from potato and tomato
Hev b 7.02		C	++ → P[a]	
Hev b 8	Profilin	C	+	Partial sequence homology with profilin from other sources
Hev b 9	Enolase (glycolytic enzyme)	C	+	Medium cross-reactivity with molds
Hev b 10	Mn superoxide dismutases	B	+	Medium cross-reactivity with molds
Hev b 11	Chitinase, hevein-like protein	B	+	Allergen possibly responsible for cross-reactivity with food allergens → "Latex-fruit syndrome"
Hev b 12	Lipid transfer proteins (LTP)	B	+	Cross-reactivity with LTP from fruits, vegetables, nuts, pollen
Hev b 13	ENSP (esterase)	B	+++ → HCW[b]	
Hev b 14	Chitinase, hevamine			

RPP, rubber particle protein; B, B-serum proteins (extra-cytosolic); C, C-serum proteins (cytosol fraction of latex); +, mild; ++, moderate; +++, strong
[a]P, patients with congenital malformations
[b]HCW, health-care workers

history of hay fever, allergic asthma, or atopic eczema and/or immediate-type sensitization to common aeroallergens such as cat dander, house dust mite, or grass pollen). Since gloves and other devices made of latex are widely used in medicine, health-care workers and patients with congenital malformations (e.g., spina bifida, urogenital abnormalities), who need frequent or continuous medical care, have been found to be particularly affected.

When the latex allergy epidemic had reached its peak, up to 17 % of health-care workers (Agarwal and Gawkrodger 2002) and 20–72 % of patients with spina bifida (Taylor and Erkek 2004) were found to be allergic to latex. An increased frequency was also evident in rubber

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industry workers. Among unselected adults undergoing surgical procedures in Germany, more than 1 % were found to suffer from latex allergy (Ruëff et al. 2001). A similar incidence of latex allergy was found in the general population of France (Bousquet et al. 2006).

Throughout the following years, the costs, which the statutory accident insurances had to bear for compensation of affected workers, significantly increased in many countries forcing specific countermeasures. Due to measures of primary prevention, the frequency of immediate-type allergy to latex fell significantly. Today, latex allergy is still present in subjects who got sensitized before the implementation of countermeasures. New cases of latex allergy occur mainly in atopic subjects being intensely exposed to the allergen.

Diagnostics

History, skin testing, determination of specific IgE antibodies in the serum, and challenge tests are the standard tools to diagnose an immediate-type allergy. For skin testing, the use of standardized skin test extracts is recommended. The raw latex milk may be also used but can evoke false-negative (ammoniated) reactions or systemic anaphylactic symptoms. Use of recombinant molecular latex allergens may improve measurement of latex-specific IgE antibodies in the serum.

Challenge tests can be performed using suspected material, which releases latex allergens. Alternatively, conjunctival or nasal challenge tests are possible using incremental concentrations of diluted skin test extracts.

Treatment/Management

Primary Prevention: In order to prevent de novo sensitization to latex, individuals presenting with a significant atopic disease (or with hand dermatoses) should avoid exposure to latex allergens. A general ban of medical gloves made of latex is not recommended, as they tend to be stronger, more flexible, and are better accepted by health-care workers (Palosuo et al. 2011). Banning of powdered latex gloves and reducing the amount of allergens in latex products are the cornerstones for preventing latex sensitization and allergy (Wrangsjö et al. 2012).

Management of Patients Suffering from Latex Allergy: Allergen avoidance is the mainstay of treatment (Taylor and Erkek 2004). Patients or workers with latex allergy have to avoid any latex exposure. Non-latex alternatives should be practiced for all skin contacts involving latex allergic individuals. Use of non-powdered latex gloves in the environment of latex allergic subjects (working place or medical environment) will significantly reduce the allergenicity of the gloves and will prevent airborne symptoms. Within a few years after these preventive measures had been started, the intensity of latex sensitization in latex allergic health-care workers significantly decreased (Ruëff et al. 2004).

An emergency kit should be provided to patients with a history of anaphylaxis upon exposure to low amounts of latex allergens and/or with a reaction to hidden allergens (e.g., food contaminated by handling with latex gloves). The emergency kit contains antihistamines and corticosteroids for oral treatment and an epinephrine injector.

Specific immunotherapy with latex was effective in small cohort studies (Tabar et al. 2002; Lasa Luaces et al. 2012). However, this type of therapy is not yet available and probably never will be. Because of the excellent results of primary and secondary prevention, the development of licensed products will presumably not be pursued.

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Single-Plex Immunoassays and Autoanalyzers

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Synonyms

ELISA; FEIA; HytTECH-288; IEMA; Immulite; ImmunoCAP; MAST; RAST; RIST

Definition

Single-plex immunoassays are procedures used in laboratories to detect and quantify individual analytes (antigens or antibodies), one specificity at a time. They involve the manual or computer-automated mixing of individual antigen and antibody reagents together at different steps throughout the assay to permit immune-complex formation and ultimately generation of a final isotopic, colorometric, fluorescent, or chemiluminescent response signal. The measured response is either proportional (noncompetitive binding) or inversely proportional (competitive binding) to the analyte's concentration following interpolation from a reference curve. This section will use IgE as the model analyte for illustration.

Introduction

The first immunoassay was reported in 1968 for the measurement of human insulin (Berson and Yalow, 2006). They described a competitive-binding reaction in a series of test tubes containing radiolabeled and unlabeled insulin for limited insulin-specific IgG antibody binding sites. The more (unlabeled) insulin in a specimen, the less

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radioactive insulin would bind to antibody. Thus, the final radioactivity response measured was inversely proportional to the concentration of the insulin in the standard or unknown serum. From this origin, many modifications of this basic immunoassay format have been developed over the years. One widely used modification has been the noncompetitive assay format in which a solid-phase anti-insulin binds insulin from serum. Then, following a buffer wash, bound insulin is detected with a second radiolabeled antibody to insulin that binds to a different determinant or epitope on the insulin molecule. This noncompetitive-binding immunoassay that uses an unlabeled immobilized capture antibody and a labeled detection antibody is called a two-site immunoradiometric assay to distinguish it from the single antibody-dependent competitive-binding radioimmunoassay. In later years, the isotopic labels have been replaced by non-isotopic labels that involve the coupling of enzymes or fluorescent molecules to the detection antibody. The use of non-isotopic labels has increased the shelf life of the reagents and reduced the hazard associated with radioisotope use and disposal.

Radioimmunosorbent Test and Radioallergosorbent Assay

By 1967 when IgE was discovered, two noncompetitive solid-phase radioimmunoassays called the radioimmunosorbent test (*RIST*) for total serum IgE and the radioallergosorbent test or *RAST* for allergen-specific IgE had been developed as a modification to the Berson and Yalow immunoassay format (Wide et al. 1967). In its original form, the RIST used an antihuman IgE coupled to a paper disk solid phase to bind IgE, and following a buffer wash, a second radioiodinated antihuman IgE was used to detect bound IgE on the disk. The RIST was cross-calibrated against the WHO IgE Reference preparation, and this assay became the primary method for measuring total serum IgE for many years. As a modification of the RIST, the RAST employed a paper disk solid phase to which allergenic molecules typically prepared as crude extracts of biological materials were covalently attached to make an allergosorbent. Once serum was added, allergen-specific antibodies of any isotype (primarily IgE, IgG, IgA) would bind to the immobilized allergen. Following a second buffer wash to remove unbound serum proteins, bound IgE was detected with ^{125}I-labeled polyclonal antihuman IgE. RAST results were reported in log-related classes or in arbitrary units following interpolation from an IgE anti-birch pollen reference curve. Since IgE antibodies to hundreds of different allergen specificities were interpolated from the IgE anti-birch reference curve, this process was called heterologous interpolation (Matsson et al. 2008). The term reflects the fact that the reference curve was constructed with dilutions of IgE antibody to a different specificity (birch pollen) than those being detected in the test sera. The original assay assigned increasing levels of IgE antibody detected to arbitrary classes. The isotopic form of the RIST and RAST and the use of classes to report IgE antibody levels are now considered antiquated and they should no longer be used.

MAST, ELISA, IEMA, FEIA

Over the years, modifications of the paper disk-based RAST assay have been commercialized. The multi-thread allergosorbent test or *MAST* replaced the paper disk with individual cellulose threads. The MAST was configured in a pipette in which serum was drawn up, left to react with different allergens on individual threads, and then unbound serum proteins were washed out with buffer. An isotopic or non-isotopically labeled anti-IgE detection antibody was then drawn into the pipette to detect bound IgE antibody. Following a final buffer wash, remaining radioactivity and enzyme-generated chemiluminescence were detected on film and the density was shown to be proportional to IgE antibody concentration the original serum.

Other groups replaced the plastic pipette with a plastic microtiter plate and configured the assay into an enzyme-linked immunosorbent assay (*ELISA*) *or* a fluorescence enzyme immunoassay (*FEIA*)

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for allergen-specific IgE or a two-site immunoenzymetric assay or *IEMA* for total serum IgE. The ELISA used allergen that had been adsorbed onto plastic wells in the microtiter plate. Following serum addition, antibodies would bind and allergen-specific IgE would finally be detected after a buffer wash with enzyme-labeled antihuman IgE. This assay works poorly with crude allergen extracts since the plastic plate has minimum protein-binding capacity and the percentage of the total protein that contains allergens is sometimes very low. The IEMA uses a microtiter plate adsorbed capture anti-IgE and an enzyme-labeled detection antibody to detect total serum IgE in a chemistry similar to the RIST.

Autoanalyzers

ImmunoCAP, *IMMULITE*, and *HYTEC 288* are 3 present-day autoanalyzers that are designed to quantify IgE antibody to over 200 allergen specificities. Their chemistries are patterned after the early RAST assay. The ImmunoCAP by Thermo Fisher Scientific [UniCAP100, ImmunoCAP 250] uses a cellulose sponge matrix in the form of a small cap as an allergosorbent on which allergen is covalently coupled. The IMMULITE System from Siemens uses a biotinylated allergen that is bound to an avidin-solid phase. The HYTEC 288 System from HYCOR/Agilent Technologies uses a cellulose wafer on which allergen is covalently coupled. All three systems are performed on computer-driven autoanalyzers to maximize precision and minimize assay turnaround time. All three of these autoanalyzers are calibrated using a heterologous total serum IgE calibration curve that is referenced to the WHO total IgE serum standard (Matsson et al. 2008). While the analytical sensitivity (0.1 kUa/L), precision, and reproducibility of these three autoanalyzers are all comparable, they measure different populations of allergen-specific IgE antibody which makes their reported quantitative allergen-specific IgE results noninterchangeable (Hamilton 2010).

Each of the autoanalyzers offers a multi-allergen screen version which is a single qualitative IgE antibody assay that detects IgE antibody that is specific for 10–15 indoor and outdoor aeroallergens that induce the majority of aeroallergen-related allergic disease. A pediatric version of the multi-allergen screen is designed to also detect IgE antibody to a number of important food allergen specificities (e.g., milk, egg, peanut, wheat, soybean). Manufacturers intentionally have chosen not disclose which allergen specificities are on their multi-allergen sorbent so that the clinician cannot use the information directly to treat the patient without further clinical assessment and IgE antibody testing. A negative multi-allergen screen result reduces the probability that IgE-mediated allergic disease is involved in the patient's clinical problem (Wickman et al. 2003).

Summary

Single-plex immunoassays that measure a single analyte, one at a time, have evolved from early radioimmunoassays into computer-controlled non-isotypic autoanalyzers that maximize performance (analytical sensitivity and specificity, precision and reproducibility, linearity/parallelism) and minimize turnaround time for obtaining results. While the three current IgE antibody autoanalyzers display comparable analytical sensitivities (0.1 kUa/L or 0.24 ng/mL) and excellent precision and reproducibility, they measure different populations of IgE antibody, and thus while their reported results are qualitatively comparable, they are not quantitatively equivalent. The use of multi-allergen solid phases in a single-plex assay format to screen sera for IgE antibody to principal aero- and food allergens that induce the majority of the aeroallergen- and food-allergen-induced allergic disease allows effective assessment of populations for atopic status.

Cross-References

- ▶ Analytes and Biomarkers: IgE
- ▶ Assay Performance Parameters
- ▶ Cow's Milk Allergy
- ▶ Diagnostic Assay Components

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▶ Egg Allergy
▶ Food Allergies, Diagnostic Testing
▶ Food Allergy, Overview
▶ IgE Testing
▶ Imported Fire Ant Allergy
▶ Peanut Allergy

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Specific IgE

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Definition

Immunoglobulins of the IgE heavy chain isotype that are specific for a given antigen/allergen.

Specific IgE

Allergen-specific IgE is the end product of allergen-specific naïve B cells that underwent class switch recombination (CSR) and plasma cell differentiation. At the plasmablast stage, B cells start secreting immunoglobulins, which reach the circulation. Some of these plasmablasts can become long-lived plasma cells, which reside in tissues (primarily the bone marrow) for many years from where they secrete immunoglobulins. This long-term production of immunoglobulins does not require persistent exposure to antigens (Radbruch et al. 2006). The presence of such long-lived plasma cells is a complicating factor for the treatment of allergies since there is no therapy available that targets these bone marrow resident plasma cells. Therefore, once allergen-specific IgE-producing long-lived plasma cells are generated, there is constant production of allergen-specific IgE that is independent of allergen exposure.

Serum concentrations of IgE are typically very low and represent less than 0.05 % of the total immunoglobulin pool. Free IgE has a relatively short half-life of around 2 days. Despite its low abundance, allergen-specific IgE is a key mediator of the type I hypersensitivity reaction. Circulating allergen-specific IgE antibodies bind to high affinity IgE receptors (FcεRI) on the surface of circulating basophils and tissue-resident mast cells as well as antigen-presenting cells. These cell surface–bound IgE molecules have a long half-life (up to several months). Upon subsequent encounter with a polyvalent allergen to which the specific IgE was generated, FCεRI on mast cells and basophils are cross-linked, leading to the release of several preformed inflammatory mediators including histamine, lipid mediators, leukotrienes, chemokines, and cytokines which cause the symptoms of the type I hypersensitivity reaction (Larche et al. 2006). Allergen-specific IgE bound to FCεRI on the surface of antigen-presenting cells greatly facilitates the capacity to bind and internalize allergens, leading to enhanced antigen-presenting capacity of these cells.

Methods to Determine the Presence of Specific IgE

There are several different methods to assess the sensitization status of an individual. In vitro tests for detection of specific IgE are frequently

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used for this purpose. Specific IgE in circulation is typically measured for diagnostic purposes using immunoassays. Recently microarray-based methods have been developed which allow simultaneous assessment of IgE specific for multiple allergens. This approach has the advantage that it requires only a small amount of serum to measure IgE antibodies of different specificities in a single test (Hiller et al. 2002). The presence of allergen-specific IgE in circulation does not necessarily imply that a patient will show clinical symptoms when exposed to this allergen since this depends on the capacity of an allergen to cross-link FCεRI-bound IgE molecules. One method to assess this capacity is the basophil activation test (BAT) in which a blood sample from a patient is incubated with allergen and basophil activation is measured by flow cytometry. Despite its high sensitivity, BAT is currently not routinely performed for diagnostic purposes. This is mainly because the method has not been sufficiently standardized to guarantee reliable and reproducible results in different institutions.

Besides in vitro methods for measuring the allergen-specific IgE in serum, in vivo skin tests are frequently used to assess the sensitization status of an individual. In vivo skin testing is generally more sensitive than in vitro assays to measure serum IgE. Skin testing is typically done by injecting antigen into the epidermis (prick-puncture test) or into the dermis (intradermal test). When an individual is sensitized to a given allergen, the typical reaction to a skin test consists of an immediate reaction followed by a late-phase reaction (LPR). The immediate reaction, which starts within minutes after application of the allergen, is the result of degranulation of skin-resident mast cells. This leads to a wheal and flare reaction that can be observed macroscopically. The LPR starts 4–8 h after allergen exposure and is characterized by swelling of the skin. The LPR is initiated by cytokines and chemokines that were released by mast cells during the immediate reaction. These factors facilitate the recruitment of activated T cells, eosinophils, and neutrophils to the site of the reaction. Tissue-infiltrating CD4+ T cells play an important role in the LPR through production of cytokines.

Skin Prick Test (SPT) are generally regarded as the method of choice to diagnose clinically relevant sensitization to a given allergen. There are some considerations that need to be taken into account when deciding to perform SPT. Under some circumstances, SPT may give false-negative results. SPT may, for example, be affected by the use of drugs like antihistamines, which suppress the histamine response. In contrast, circulating IgE levels are normally not affected by such treatments. Furthermore, there are several risks associated with SPT. There is a chance for systemic reactions in response to SPT, especially with certain anaphylactogenic allergens. On the other hand, since allergens are presented to the immune system, SPT can lead to de novo sensitization to allergens to which the patient was not sensitized before the therapy.

Cross-Reactivity

IgE that specifically binds to a given antigen (antigen A) can be the product of a plasma cell originating from a B cell that was activated in response to antigen A. It is however also possible that this IgE is the product of a plasma cell originating from a B cell that was activated in response to a different antigen (antigen B) that shares some degree of homology with antigen A. This phenomenon is referred to as IgE cross-reactivity. IgE immunoglobulins that were raised against a certain allergen can sometimes be cross-reactive to other antigens. Homologous allergens from phylogenetically related organisms are often cross-reactive. Such allergens have a high degree of sequence homology, resulting in similar three-dimensional protein structures that can have identical conformational epitopes. On the other hand, several allergens that are only distantly related show strong cross-reactivity (Aalberse et al. 2001). It can be of importance for therapeutic purposes to know the allergen that initiated the production of specific IgE antibodies. This initiating allergen will have the broadest range of IgE epitopes and therefore have the broadest therapeutic effect when used in allergen-specific immunotherapy.

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Cross-References

- ▶ Activating and Inhibitory Receptors on Mast Cells
- ▶ Analytes and Biomarkers: IgE
- ▶ Basophils
- ▶ Diagnostic Components: Allergen for In Vivo (Skin Testing, Immunotherapy) and In Vitro (Serology) IgE Antibody Testing

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Sublingual Immunotherapy

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Synonyms

Allergen immunotherapy; Allergen-specific desensitization; Allergy drops; Allergy immunotherapy; Hyposensitization; Immunotherapy

Definition

Sublingual immunotherapy involves the administration of specific allergens by placement of allergen extract in a liquid or tablet formulation under the tongue for 1–2 min followed by swallowing (Canonica et al. 2009) and is conducted for the purpose of lessening or preventing the allergic symptoms due to exposure to those specific allergens (Cox et al. 2011).

Background

Conventional subcutaneous immunotherapy is an effective treatment option for many allergic diseases such as allergic rhinitis, allergic asthma, and Hymenoptera allergy. Despite the benefits of subcutaneous immunotherapy, not all individuals improve, significant time and expense may be involved, and the risk of adverse reactions, such as anaphylaxis, remains (Casale and Stokes 2011). Thus, other forms of immunotherapy have been explored, and sublingual immunotherapy is being increasingly used worldwide. Sublingual immunotherapy is currently commercialized and used in most European and South American countries as well as in Australia and Asia. However, sublingual immunotherapy is not approved for use by the Food and Drug Administration of the United States (US) and is not currently recommended for clinical practice in the United States. Several aspects of sublingual immunotherapy are under investigation, including optimal dosing, duration of treatment, mechanisms of action, preventive effects, and efficacy. Numerous clinical trials are ongoing to further define the parameters and guidelines for the use of sublingual immunotherapy (Canonica et al. 2009).

Clinical Indications

In general, immunotherapy should be considered for individuals who demonstrate evidence of allergic sensitization to applicable environmental allergens and have symptoms of allergic rhinitis or asthma after allergen exposure (Cox et al. 2011).

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As noted previously, specific guidelines for the use of sublingual immunotherapy are not yet firmly established.

Efficacy

A meta-analysis of 60 randomized, blinded, placebo-controlled studies of sublingual immunotherapy for allergic rhinitis was conducted which pooled 2,333 patients receiving sublingual immunotherapy and 2,256 patients receiving placebo. Overall, participants receiving sublingual immunotherapy had a significant reduction in symptoms (SMD −0.49; 95 % confidence interval (CI) −0.64 to −0.34), $P < 0.00001$) and in medication requirements (SMD −0.32; 95 % CI −0.43 to −0.21), $P < 0.00001$) compared to placebo. None of the trials in this analysis reported severe systemic reactions or anaphylaxis (Radulovic et al. 2010).

Another meta-analysis reviewed the clinical efficacy of sublingual immunotherapy for the treatment of asthma. Twenty-five randomized controlled trials were included in this review involving 1,706 patients. Sublingual immunotherapy was seen to significantly reduce asthma severity in terms of categorical outcomes. For this, all outcomes were analyzed together including asthma symptoms, medication use, and respiratory function test results. However, when asthma symptoms were analyzed using continuous outcomes by standardized mean differences, there was a trend toward improved asthma outcomes favored by sublingual immunotherapy, but without statistical significance (Calamita et al. 2006).

Nieto et al. studied the results of five published meta-analyses reviewing the efficacy of sublingual immunotherapy for the treatment of allergic asthma and allergic rhinoconjunctivitis. The five meta-analyses included 43 studies, 17 of which were used in more than one meta-analysis. Numerous discrepancies were found in the data used for the meta-analyses. The results used differed from the original study to those used in the meta-analysis or across meta-analyses many times. There were also inconsistencies among the meta-analyses in the reported benefits when considering factors such as age, disease, allergen, symptoms, and medication use. Due to these discrepancies and inconsistencies, there was a lack of robustness among the meta-analyses, and this review concluded that there was not enough evidence to support sublingual immunotherapy as a routine treatment option for patients with allergic asthma and allergic rhinoconjunctivitis (Nieto et al. 2009).

Conclusion

Sublingual immunotherapy is becoming increasingly prescribed around the world and in several European countries is the standard of care for patients with allergic diseases who are treated with immunotherapy. A substantial number of clinical studies have demonstrated the efficacy of sublingual immunotherapy, but a great deal of heterogeneity exists in the designs of these studies, making it difficult to assess the value of sublingual immunotherapy accurately (Casale et al. 2009). More studies are needed to further evaluate the parameters and benefits of the use of sublingual immunotherapy, especially when compared to subcutaneous immunotherapy.

Cross-References

- Allergen Immunotherapy, Overview
- Immunotherapy for Allergic Rhinitis
- Immunotherapy for Asthma
- Immunotherapy for Hymenoptera Allergy
- Immunotherapy with Recombinant and DNA-Conjugated Allergens
- Immunotherapy, Mechanisms
- Safety of Immunotherapy

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Testing: DLCO

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Synonyms

Carbon monoxide uptake; Diffusing capacity

Definition

DLCO stands for diffusing capacity of the lungs for carbon monoxide. It provides a measurement for carbon monoxide (CO) transfer from the airways, across the alveolar-capillary membrane, into the pulmonary capillaries, and across the red blood cell membrane where CO then binds to hemoglobin (Hegewald and Crapo 2010).

Background

Conditions associated with an abnormal DLCO include interstitial lung disease, chronic obstructive pulmonary disease, and pulmonary vascular disease (see Table 1). The test is typically performed in subjects using an office spirometer, a gas analyzer, and a source of test gas. The most common technique utilized is a single-breath maneuver where the subject inhales rapidly to total lung capacity (TLC) using only minimal effort and then holds their breath for approximately 10 seconds (MacIntyre et al. 2005).

The Use of Carbon Monoxide

The goal of a diffusing capacity analysis is to measure the status of the alveolar-capillary membrane. However, the uptake of most soluble gases is influenced by pulmonary blood flow (Enright 2012). CO binds to hemoglobin with an affinity 200–250 times that of oxygen (Hegewald and Crapo 2010). In addition, hemoglobin has a high amount of available CO binding sites. These factors result in low pulmonary capillary CO tension and CO uptake is therefore diffusion limited and less dependent on pulmonary blood flow/cardiac output. Diseases that cause poor diffusion of oxygen will also result in poor diffusion of carbon monoxide (Enright 2012).

Indications

DLCO helps in developing a differential diagnosis for a variety of pulmonary conditions. It can also be used to follow disease severity/progression over

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Testing: DLCO, Table 1 Conditions associated with abnormal DLCO

Physiological	Pathological
Reduced DLCO	*Reduced DLCO*
Inspiratory muscle weakness	Anemia
Reduced effort	Pulmonary emboli
Valsalva maneuver	Cigarette smoking (reduced Hb binding sites and increased CO back pressure)
	Increased inspired fraction of oxygen (patient receiving supplemental oxygen)
	Emphysema
	Interstitial lung disease
	Pulmonary edema
	Pulmonary vasculitis
	Pulmonary hypertension
Increased DLCO	*Increased DLCO*
Decreased inspired fraction of oxygen (altitude)	Polycythemia
Müller maneuver	Left-to-right shunt
Exercise	Pulmonary hemorrhage
Supine position	Asthma
Obesity	

Adapted from MacIntyre et al. (2005)

time. DLCO is predictive of mortality in the general population, as well as in patients who have undergone pulmonary resection (Pellegrino et al. 2005).

Interpretation

Typically, DLCO is performed along with spirometry and lung volumes, as abnormalities in DLCO can be better interpreted if they are in conjunction with a restrictive, obstructive, or normal pulmonary function pattern. Technical guidelines and correction factors must be taken into account (MacIntyre et al. 2005; Crapo et al. 2001). The lower limit of normal is typically the 5th percentile of the reference population. The American Thoracic Society has published a grading scheme for severity of DLCO reduction (Pellegrino et al. 2005). Mild reduction is less than the lower limit or normal but still greater than 60 % predicted. Moderate reduction is between 40 % and 60% predicted and severe less than 40 % predicted. Table 2 subdivides DLCO findings in the context of spirometry values.

Testing: DLCO, Table 2 Interpretation of DLCO and Spirometry

	Obstructive	Restrictive	Normal
Normal/ increased	Asthma	Chest wall disorders	
	Chronic bronchitis	Neuromuscular disorders	
Reduced	Emphysema	ILD	Pulmonary vascular disorders
		Pneumonitis	Anemia
			Early ILD

ILD Interstitial lung disease (Pellegrino et al. 2005)

Cross-References

► Diseases in DDx of Asthma: COPD

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Testing: High-Resolution Chest Computed Tomography Scan

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Synonyms

HRCT; Thin-section CT scan

Definition

High-resolution computed tomography (HRCT) chest scan is a powerful diagnostic tool for the evaluation of lung parenchyma. It can identify a wide array of findings that cannot be found with standard chest radiography or conventional helical CT scans. HRCT utilizes a high spatial frequency algorithm (bone) and thin 1 mm collimation, allowing for visualization of secondary pulmonary lobules and often interlobar fissures (Stark 2013).

Indications

The clinical indications for HRCT include the following: to aid with diagnosis in patients with nonspecific radiographic abnormalities, to confirm/exclude diffuse pulmonary disease in patients with functional abnormalities or normal/equivocal findings on other radiographic studies, and to potentially determine disease prognosis. In the setting of pulmonary fibrosis, disease reversibility is typically suggested by extensive ground-glass opacification; irreversible changes are more likely if honeycombing, a reticular pattern, or architectural distortion is present) (Hansell et al. 2010).

Other clinical uses for HRCT are to investigate potential etiology of hemoptysis, examine unexplained severe obstructive airways disease or likely bronchiectasis, determine feasibility for possible lung volume reduction surgery (by determining emphysema distribution), and inform a future lung biopsy (Hansell et al. 2010). In regard to lung biopsy, HRCT can demonstrate optimal location and necessary type (e.g., bronchoscopic versus surgical), and there is a high degree of correlation between radiographic and eventual histopathologic findings (Stark 2013). Finally, HRCT is useful for quantifying the extent of diffuse lung disease to assess treatment efficacy (Naidich and Ko 2010). Conventional helical CT scanning is the modality of choice for assessment of disease of the mediastinum. For many other situations, such as evaluation of diffuse pulmonary disease, emphysema, bronchiectasis, pulmonary nodules, and metastatic lesions, HRCT is superior. There are no absolute contraindications to HRCT, although care must be taken in pregnant or potentially pregnant women (Wagner and Applegate 2008).

Sensitivity and Specificity

HRCT can be far more informative than chest radiography or conventional CT scanning. Its sensitivity and specificity are 95 % and nearly 100 %, respectively (Mathieson et al. 1989), and it allows for a confident diagnosis about 50 % of the time; this diagnosis is eventually proven accurate at a rate of approximately 93 %. For evaluation of diffuse pulmonary disease, chest radiography has a sensitivity of 80 % and specificity of 82 %. In addition, it allows for a confident diagnosis only 23 % of the time, with these initial assessments proven to be accurate at a rate of 77 % (Mathieson et al. 1989). Chest radiography also appears unremarkable in up to 15 % of symptomatic infiltrative lung disease cases, up to 30 % of bronchiectasis patients, and nearly 60 % of the time in emphysema (Epier et al. 1978).

HRCT Diffuse Pulmonary Disease Patterns

There are a number of important factors to consider when placing HRCT in the clinical

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context: the patient's clinical history (especially disease duration and immune status) and particular radiologic findings (predominant anomaly pattern, distribution, and associated features). As a generalization, the main HRCT patterns are reticular/short nodular opacities, nodular opacities, parenchymal opacification, and cystic pulmonary disease/decreased attenuation (Hansell et al. 2010). Associated features may include calcifications, effusions, thickening, pleural plaques, and lymph node enlargement.

Reticular

The reticular pattern on HRCT is generally due to interstitial disease, indicating abnormalities in the loose interstitial connective tissue pulmonary network (bronchovascular, subpleural/sub-fissural, and alveolar-septal). Reticular subtypes include thickened interlobular/intralobular septa, perilobular thickening, conspicuous remnant septa, honeycomb (intermediate), or other various causes of advanced cystic pulmonary disease and intersecting linear opacities (Hansell et al. 2010).

Nodular

The nodular pattern on HRCT is encountered in either interstitial or airspace diseases (Hansell et al. 2010). It can be classified by distribution (centrilobular, perilymphatic, airspace, or perivascular) or appearance (airspace nodules typically have fuzzy margins, while interstitial nodules are described as having sharp, unsharp, or stellate margination) (Stark 2013).

Broadly speaking, if small nodules are in contact with pleura or fissures on HRCT, then a diagnosis of sarcoidosis (if nodules are clustered), lymphangitic carcinomatosis (if interlobular septa are concurrently thickened), or silicosis is probable. On the contrary, if such nodules are not directly adjacent to pleura or fissures, then infection or tumor that has hematogenously spread is likely (Stark 2013). In these cases, presence of a "tree-in-bud" pattern (branching structures resembling a budding tree) suggests infectious bronchiolitis or aspiration; otherwise, hypersensitivity pneumonitis or respiratory bronchiolitis are more likely (Hansell et al. 2010).

Centrilobular nodules are typically somewhat removed from pleural surfaces (5–10 mm) and surround small vessels. Associated diseases include hypersensitivity pneumonitis (HP), sarcoidosis, Langerhans cell histiocytosis, and bronchiolitis; a tree-in-bud pattern may be seen in aspiration or infectious bronchiolitis. Airspace nodules may also indicate aspiration or infectious bronchiolitis, as well as diffuse panbronchiolitis or tuberculosis. While also having a centrilobular location and capable of displaying a tree-in-bud pattern, airspace nodules are larger than corresponding centrilobular nodules (Stark 2013).

On the other hand, perilymphatic nodules are subpleural and often cluster, potentially creating pseudo-plaques. Silicosis, lymphangitic carcinomatosis, and sarcoidosis may cause perilymphatic nodule formation. Lastly, if nodules are subpleural but diffusely distributed, they are labeled random or perivascular. Their uniform location is usually due to hematogenous dissemination from tumor metastasis, septic emboli, or miliary infection (e.g., fungal disease or tuberculosis) (Stark 2013).

Parenchymal Opacification

Large confluent opacities on HRCT indicate inflammation or infection that has caused lung parenchyma to take on increased attenuation. The main two subtypes are consolidation and ground-glass opacification. Consolidation, also known as airspace filling, is defined as opacification of lung parenchyma that compromises visualization of anatomy (such as vascular structures) and results in air bronchograms (air-filled bronchi being made visible by opacification of surrounding alveoli) (Wong et al. 1994). Ground-glass opacification has

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opacification without either of these features (Remy-Jardin et al. 1993).

Consolidation is the result of filling of areas that normally contain alveolar gas; this can be due to blood, cells, edema, pus, or surfactant. The differential diagnosis includes pneumonia, edema, or hemorrhage in the acute setting; bronchioloalveolar carcinoma and cryptogenic or eosinophilic pneumonia are potential chronic etiologies (Stark 2013).

In contrast, ground-glass opacification results when there are abnormalities of lung parenchyma smaller than HRCT can resolve. This pattern is seen in a number of settings: partial alveolar collapse, incomplete alveolar filling, increased pulmonary capillary volume, and early interstitial pulmonary disease; in the latter case, traction bronchiectasis may also occur (Stark 2013). Pulmonary function measures such as diffusion capacity for carbon monoxide (DLCO) may be concurrently reduced. The differential diagnosis for this pattern depends on whether the ground-glass opacities are acute or chronic, focal, or diffuse. Acute focal etiologies include fibrosis, atelectasis, or inflammation; atypical alveolar hyperplasia is another consideration. When focal abnormalities persist and become chronic, bronchioloalveolar carcinoma is a concern (if the lesion is sufficiently large) (Hansell 2010). Diffuse ground-glass opacities in the acute setting may be due to pulmonary hemorrhage or edema, pneumonia, drug reactions, eosinophilic lung disease, and HP. HP may also cause chronic diffuse ground-glass opacification, as can pneumonias (nonspecific interstitial, desquamative interstitial, or organizing), sarcoidosis, bronchioloalveolar carcinoma, and respiratory bronchiolitis-associated interstitial lung disease (Miler and Shah 2005).

Decreased Attenuation

In contrast to the various presentations of increased attenuation detailed above, decreased attenuation is usually due to one of two causes: emphysema or air trapping due to small airways disease (e.g., asthma) (Hansell et al. 2010). More rarely, it can be seen in other diseases such as cystic lung disease, bronchiolitis obliterans, and pulmonary hypoperfusion (such as in severe pulmonary arterial hypertension). It can even be present as a diffuse non-pathologic finding in elderly patients (Stark 2013).

Mosaic Attenuation

Mosaic attenuation describes an HRCT pattern of lung parenchyma with varying areas of increased and decreased attenuation. This can be seen when diseased lung is intermixed with normal lung or when there are areas of varying vascular perfusion or hypoxic vasoconstriction (from airway abnormalities) (Worthy et al. 1997).

Cystic Airspaces

Finally, cystic lung disease is indicated when HRCT shows air-containing (low attenuation) areas clearly demarcated by visible walls (Hansell et al. 2010). This pattern is the dominant feature of a variety of diseases, including Langerhans cell histiocytosis, lymphangioleiomyomatosis, bullous emphysema, infective pneumatoceles, established pulmonary fibrosis, and other rare diffuse pulmonary diseases (Hansell et al. 2010).

Disease Distribution

After parenchymal disease pattern, disease distribution is another important factor to consider in HRCT interpretation (Sundaram et al. 2008). It is important to note whether affected lung parenchyma is predominantly diffuse or focal; if focal, the next step is to determine if abnormalities are central or peripheral, anterior or posterior, and apical or basal (Stark 2013).

Diffuse parenchymal lung disease indicates lymphangioleiomyomatosis or advanced pulmonary disease. If disease is largely found in the

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central areas of the lung, lymphoma, Kaposi's sarcoma, sarcoidosis, or lymphangitic tumor are likely. On the other hand, if peripheral lung parenchyma is more involved, then collagen vascular diseases, drug reactions, graft-versus-host disease, eosinophilic lung disease, asbestosis, idiopathic pulmonary fibrosis, and organizing or desquamative interstitial pneumonia are of concern (Stark 2013).

Apical disease suggests granulomatous diseases, pneumonoconioses, and Langerhans cell histiocytosis; basal involvement is more typical of pulmonary diseases with fibrosing properties. If the affected lung parenchyma is anterior, acute respiratory disease syndrome with diffuse alveolar damage is probable. The differential diagnosis for posterior involvement depends on whether the abnormalities are predominantly superior or inferior. Causes of posterosuperior involvement include silicosis and reactivation of fungal or mycobacterial infections, whereas posteroinferior disease raises concern for aspiration pneumonia, asbestosis, and hydrostatic pulmonary edema (Stark 2013).

Signs of Airway Disease

HRCT can also be useful for assessment of disease of the airways, both small and large. Bronchiectasis, the most commonly encountered large airways disease, indicates chronic irreversible bronchial dilation (Hansell et al. 2010). On the other hand, small airway diseases can be from a variety of causes, including constrictive bronchiolitis (bronchiolar scarring and constriction, possibly after a viral lower respiratory tract infection) and exudative bronchiolitis (Müller and Miller 1995).

Conclusion

HRCT is an invaluable tool for accurate assessment of lung parenchyma and is more sensitive and specific than both standard chest radiography and conventional helical CT scanning. When placing HRCT in the clinical context, predominant anomaly pattern and disease distribution need to be compared with a particular patient's clinical history.

Cross-References

- Autoimmune Lung Disease
- Bronchiectasis
- Idiopathic Acute Eosinophilic Pneumonia
- Idiopathic Pulmonary Fibrosis

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Testing: Sputum Eosinophil Count

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Synonyms

Airway inflammation; Sputum cell count

Definition

Sputum is a respiratory expectorant composed primarily of mucus and does not contain nasopharyngeal secretions or saliva. The sputum eosinophil count refers to the number of eosinophils in sputum, typically expressed as a percentage of the total cell count. Examination of sputum is a noninvasive way to assess for airway inflammation.

Collection and Processing

Sputum can be naturally produced via a productive cough or induced by inhaling bronchial irritants. Protocols for induced sputum typically involve 3 % hypertonic saline administered via nebulizer (AARC 1993; Pavord et al. 1997; National Jewish Health 2010). Oftentimes, patients are pretreated with a bronchodilator. The sample may then be treated with dithiothreitol (DTT), a mucolytic agent, to promote cell dispersion. The sample is centrifuged and subsequently undergoes Wright staining. The differential cell count is then obtained using bright field microscopy.

Sputum Eosinophilia

A normal sputum eosinophil count is ≤ 1 % (Pizzichini et al. 1996). Sputum eosinophilia typically refers to sputum eosinophil counts >2 % (Green et al. 2002). Conditions associated with elevated levels of sputum eosinophils include allergic asthma, nonallergic asthma, eosinophilic bronchitis, Churg-Strauss syndrome, and interstitial pulmonary fibrosis (Table 1). Although, sputum eosinophilia may be present in chronic obstructive pulmonary disease, this finding is atypical for this diagnosis. Charcot-Leyden crystals are a characteristic feature of airway eosinophilia. These structures are composed of eosinophil cell and granule membrane lysophospholipase and on sputum examination stand out as distinct, needle-shaped structures (Jeffery 2008; Moqbel et al. 2008).

Testing: Sputum Eosinophil Count, Table 1 Conditions associated with sputum eosinophilia

Asthma
Acute eosinophilic pneumonia
Chronic eosinophilic pneumonia
Churg-Strauss syndrome
Sarcoidosis
Idiopathic hypereosinophilic syndrome
Idiopathic pulmonary fibrosis
Connective tissue disease
Neoplasms
Nonhelminthic infections
Pulmonary Langerhans cell histiocytosis
Drug- and toxin-induced eosinophilic lung diseases
Nonsteroidal anti-inflammatory drugs (NSAIDs)
Antimicrobials
Phenytoin
Helminthic and fungal infection-related eosinophilic lung diseases
Allergic bronchopulmonary aspergillosis
Loffler's syndrome
Ascaris lumbricoides
Hookworm
Strongyloides stercoralis
Trichinosis
Cutaneous and visceral larva migrans
Schistosomiasis
Tropical pulmonary eosinophilia
Fungal pneumonia

Adapted from: Klion and Weller (2012)

Sputum Eosinophilia in Asthma

Measurement of sputum eosinophilia in asthmatics is reproducible (Bacci et al. 2002). Asthmatics are

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known to have significantly higher levels of sputum eosinophils than the general population (Jeffery 2008). Infiltration of eosinophils, along with neutrophils and T cells, is a characteristic of the late asthmatic response. After aeroallergen challenge, IL-5 -/- mice fail to develop eosinophilia (Frew 2008). Th2 cytokines contribute to the pattern of airway inflammation in asthma, including IL-5, which promotes the growth, differentiation, and activation of eosinophils.

Given the ability of sputum eosinophil count to noninvasively measure airway inflammation (Pavord et al. 1997), this measurement represents an intriguing potential biomarker to tailor asthma management. Protocols that make treatment decisions based on eliminating sputum eosinophilia have been shown to reduce asthma exacerbations in adults in comparison to guidelines-based care (Petsky et al. 2009). In a recent review, the pooled odds ratio estimate effect for any asthma exacerbation in patients managed based on sputum eosinophil count was 0.49, and the rate ratio for reduced number of exacerbations was 0.54 (Petsky et al. 2009). In addition, multiple studies have shown a significantly longer time to first exacerbation in patients receiving treatment based on sputum eosinophils (Green et al. 2002b; Chlumsky et al. 2006; Jayaram et al. 2006). In addition, the absence of sputum eosinophilia in asthmatics predicts a lack of corticosteroid responsiveness (Green et al. 2002a).

Cross-References

- ▶ Eosinophil Activation
- ▶ Eosinophil Granule Proteins
- ▶ Eosinophil Historical Background
- ▶ Eosinophil Progenitors, Growth, and Differentiation and Death
- ▶ Eosinophil Recruitment
- ▶ Eosinophil, Definition and Morphology

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Textile Allergy

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Synonyms

Allergic contact dermatitis due to textile fibers; Clothing allergy; Textile contact dermatitis

Definition

Textile allergy or textile contact dermatitis can be defined as cutaneous manifestations caused by wearing clothing.

Introduction

The manifestation of textile allergy is usually located in the skin. For that reason, it is also known as textile contact dermatitis. The etiological agents may be the fabric itself or more commonly the chemical additives used in manufacturing the clothes, e.g., textile dyes and finishing agents.

Historical Background

The first case of textile contact dermatitis was probably recognized by a group of dermatologists in the British Army, during the Second World War, who found a number of cases in some of the troops of the British Army because of wearing khaki shirts. Skin lesions such as papular, scaly, erythrodermic, and even purpuric ones were described and it was concluded that those were due to a primary irritant quality in new khaki shirts. After the Second World War, the risk and the number of cases of contact dermatitis to textiles increased due to the introduction of new synthetic materials in industry as dyes and dyeing nylon. The undyed nylon did not cause allergic reaction. Also, the use of urea–formaldehyde resins present in blouses and shirts has caused contact dermatitis in people who used them and they were sensitized to formaldehyde. Apart from dyes and formaldehyde resins, synthetic fibers may themselves cause contact dermatitis (Martin-Scott 1966).

Prevalence

Despite improvement of techniques in textile fabrication, currently, allergic contact dermatitis caused by textiles is not unusual. However, its prevalence is unclear, because studies have been performed with different design and methodology. Some studies used variables such as age, gender, history of atopy, and duration of the cutaneous symptoms and also exposure to hair dye, tattoo, contact allergy with formaldehyde, body location of the skin lesion, and type of materials of exposure.

Some studies carried out patch tests in patients with a textile series, and therefore, the prevalence data obtained concerned positive reactions to allergens included in this series.

Textile Dye

Disperse dyes (DDs) are the most common sensitizers among textile dyes. They are used for coloring mixed and synthetic materials based on fibers such as acetate, acrylics, polyamide, and polyester, or a blend of those with other fiber types; they are not used to dye natural fibers (e.g., wool, cotton, and linen). Although they are well-known contact sensitizers, they are not included in the majority of commercially available baseline patch test series (Ryberg et al. 2011). The disperse dyes are planar and fat-soluble molecules with a substituted anthraquinone or azo structure, and DDs do not chemically bond to the fibers, and their small, lipophilic molecules can therefore easily migrate on the skin surface of the person who is wearing the garment; they may be removed by rubbing

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Textile Allergy, Table 1 Classification of disperse dyes

Generic name
Disperse Black 1
Disperse Blue 1
Disperse Blue 3
Disperse Blue 7
Disperse Blue 26
Disperse Blue 35
Disperse Blue 85
Disperse Blue 102
Disperse Blue 106
Disperse Blue 124
Disperse Blue 153
Disperse Brown 1
Disperse Orange 1
Disperse Orange 3
Disperse Orange 13
Disperse Orange 37
Disperse Orange 76
Disperse Orange 149
Disperse Red 1
Disperse Red 11
Disperse Red 17
Basic Red 46
Disperse Yellow 1
Disperse Yellow 3
Disperse Yellow 9
Disperse Yellow 23
Disperse Yellow 39
Disperse Yellow 49
Disperse Yellow 54

and by exposure to water. Most of all the DDs are azo dyes followed by anthraquinone dyes. Azo dyes (Table 1) are currently employed to create almost the entire range of shades. They are cheap and easy to apply. Therefore, this dye class is used more often. Within the EU, some DDs (mainly azo) are classified as allergenic, and their use is restricted (Malinauskiene et al. 2012).

Contact allergy to textile dyes may result in a characteristic dermatitis but also in atypical signs, uncommon features, an atypical localization, and unusual clinical patterns. It could present not only like typical chronic dermatitis but also as persistent erythematous wheal-type or transient urticarial dermatitis, prurigo-like eczema, diffuse itching, erythema multiforme-like lesions, purpuric dermatitis, nummular dermatitis, erythroderma, or pseudolymphoma. The causing allergen can easily be missed if the patients are not routinely tested with textile dyes (Ryberg et al. 2006). When the diagnosis of DD-related dermatitis was unknown, patients were diagnosed with lichen simplex chronicus, parapsoriasis, mycosis fungoides, drug eruption, post-inflammatory hyperpigmentation, pigmented purpura, or scabies (Malinauskiene et al. 2012).

The dermatitis related to textile dyes can be found on the face, scalp, neck, arms, hands, trunk, leg, feet, armpit, and genital area and is widespread.

History of atopy and female sex are risk factors for cutaneous reactions. The high frequency of sensitization to DDs in women may be caused by women's tendency to wear tighter fitting clothes, lace underwear, or tights, which are always synthetic (Ryberg et al. 2009).

Contact allergy to textile dyes may be a cause of occupational dermatitis. However, the diagnosis is often missed due to the absence of textile dyes in the contact dermatitis standard batteries or due to the fact that the clinical data provided by the patient does not suggest textile dermatitis because of contact allergy.

Contact Allergy to Disperse Dyes in Children

A recently published systematic review of allergens that cause allergic contact dermatitis in children have been described, including the sensitization mentioned by several types of disperse dyes: Disperse Blue 124, Disperse Blue 106, Disperse Orange 3, Disperse Red 1, and Disperse Yellow 3. According to this review, the prevalence of positive reactions in at least 1% of tested children was found to be statistically significant only when they showed positivity in the patch test to Disperse Blue 124 but not to other DDs (Malinauskiene et al. 2012).

Prevalence of Contact Allergic Dermatitis Due to DDs

Most of the studies in patients with suspected allergy to textile materials showed positive reactions to DDs. The prevalence of contact allergy

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from disperse dyes in textiles varies with the type of population and the dyes used in patch testing. The available data indicate that prevalence of positive patch test reactions for at least three dyes (Disperse Blue106, Disperse Blue124, and Disperse Orange 3) was >1 % in screening of dermatitis patients (Malinauskiene et al. 2012).

Textile Allergy, Table 2 Classification of durable press chemical finishes for patch testing

Name
1,3-Dimethyl-4,5-dihydroxyethyleneurea
Dimethylol dihydroxyethyleneurea
Dimethylol propylene urea
Ethylene urea, melamine/formaldehyde
Melamine/formaldehyde resin
Tetramethylol acetylenediurea
Urea–formaldehyde resin

Formaldehyde Resins

Synonyms: Formaldehyde-releasing permanent press finishes, formaldehyde textile resins, textile finish resins, durable press resins, permanent press clothing finishes, formaldehyde releasers, durable press chemical finishes in textiles.

Durable press chemical finishes (DPCF) is a group of chemicals which may release formaldehyde, and after making contact with the skin, it becomes a strong allergen with great ability to produce skin sensitization.

Textile formaldehyde resins have been used on fabrics since the mid-1920s to remove wrinkles from clothes after being subjected to wear and washing, especially those garments made from 100 % cotton materials and fabrics mixed with cotton and polyester. They give textile body and improve their quality, touch, and appearance. DPCF can also facilitate bleaching and dyeing and make fabrics waterproof, nonshrinkable, and mothproof; they can ameliorate nylon and make it electrically antistatic (De Groot et al. 2010a).

Although the use of formaldehyde in textiles is known since the mid-1920s, the allergic contact dermatitis secondary to the use of formaldehyde in textiles was reported with a high number of cases in the literature during the 1950s and 1960s, because the first finishes contained large amounts of free formaldehyde, leading to allergic dermatitis after contact with clothing (Scheman et al. 1998).

In recent years, the textile industry has attempted to lower the amount of free formaldehyde in wearing apparel and bedding fabrics. This is reflected in the declining number of reported cases of patients with contact allergy to textile caused by formaldehyde (Table 2). Currently, most finishes are based on modified dimethylol dihydroxyethyleneurea, which releases less formaldehyde (De Groot et al. 2010b).

Chemistry of Formaldehyde in Clothes

Cellulose fibers and especially cotton are still the most important kind of fibers for textiles. One main disadvantage is wrinkling after washing, which is caused by swelling of the cellulosic fibres from moisture absorption. This can be solved by using durable press chemical finishes (DPCF). The current chemical approach is the reaction of multifunctional cross-linking agents with the hydroxyl groups of adjacent cellulose molecules that hinder cellulose fiber swelling. Due to the need of formaldehyde in the resin synthesis, many of the finished textiles release formaldehyde. Subsequently there is a degradation of the resin during storage, during wearing because of sweat and by acid washing, or from the use of chlorine during laundering (De Groot et al. 2010a).

Legal Aspects on the Use of Formaldehyde in Clothing and Other Textiles

To decrease the risk of allergic contact dermatitis and other side reactions to the use of textile products containing formaldehyde, some countries have adopted within their legislation to set limits to the amount of formaldehyde present in the textile industry.

In 1973, Japan was the first country which showed a significant reduction in the reporting of cases of patients sensitized to formaldehyde in subsequent years, followed by Finland, and other

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countries with legal limitations include China, Norway, France, and the Netherlands.

The limits on the content of formaldehyde vary, but usually recommended garments for babies and infants should contain <20–30 ppm formaldehyde and for clothes in direct contact with the skin a maximum of 75–100 ppm, and for clothing and textiles without direct skin, there are upper limits of 300–400 ppm formaldehyde.

The USA until 2008 had no limits on the content of formaldehyde in textiles and clothing, but thereafter the Congress of the USA passed the Consumer Products Safety Commission Modernization Act that in less than 2 years will take out a study on the use of formaldehyde in the manufacture of textiles and clothing to identify any risk to consumers.

In Europe, the textile industry may have the "European Ecolabel" when the limits of formaldehyde in textiles that are not in direct contact with the skin contain <300 ppm and those which are in direct contact with the skin <30 ppm (De Groot et al. 2010b).

Fiber Additives

Fiber additives are chemicals embedded into fibers to achieve certain characteristics in textiles and obtain special properties, such as flame retardants, delustrants, antioxidants, optical brighteners, and ultraviolet light absorbers. The allergen was an ultraviolet light absorber, 2-(2-hydroxy-5-methylphenyl) benzotriazole, which had been added to spandex fibers (Hatch and Maibach 1995).

The elastane or spandex, better known as Lycra, is a synthetic fiber with high elasticity, invented in 1959 by chemist Joseph Shivers. When it was introduced in the textile area for the first time, the spandex revolutionized the textile industry. The spandex is used in conjunction with other fibers to make fabrics to produce optimal lingerie, women's clothing, socks, tights, stockings, sportswear, and swimwear and, thanks to its elastic properties, gives freedom of movement for athletes and other people who use them.

Metallic Fibers

Metallic fibers, for example, nickel, zinc, and copper fibers, are of little used in the fabrics, especially in garments having contact with the skin, because they can be abrasive when worn (Hatch and Maibach 1995).

When fabrics are not properly rinsed after washing, soil and detergent residue may remain in the fabric.

There are few published studies on allergic contact dermatitis caused by wearing or using fabrics. Among the few allergens reported, those previously commented are an epoxy resin in a textile label, an ultraviolet light absorber in a spandex fiber, and metallic fibers in a shawl.

Textile Fabrics

The textile fabrics more known to cause allergic contact urticaria are wool, silk, rubber, and nylon. Although allergy to silk is a well-known occupational hazard in sericulture, allergy reactions to silk products are rare. Silk fiber is comprised of fibrous protein filaments, fibroin, adhered with sericin. During manufacturing and in the degumming process, the sericin of silk is usually eliminated. In products of silk fibers, sericin can be found due to incomplete degumming and contamination with material from silkworms, pupa, or cocoons.

There are different silk allergens found in nature described by Fisher: silk fiber, sericin in raw silk, and silkworm protein. Patients allergic to silk showed an early-phase reaction to silkworm cocoons and raw silk and a late-phase reaction to sericin. The cause of the contact allergic dermatitis may be because of some of these allergens persisting in silk cloths. Positive skin tests associated with clinical history consistent with allergic problem suggest that there is an immune process involved (Inoue et al. 1997).

Occupational Contact Allergy

In recent decades, few cases of occupational contact dermatitis have been reported in the

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textile industry due to formaldehyde-releasing permanent press finishes.

A medical doctor developed dermatitis attributed to a hospital gown and face mask. He was patch tested several times and reacted to formaldehyde, quaternium-15, imidazolidinyl urea, urea–formaldehyde resin, melamine/formaldehyde resin, and ethylene urea. Other studies have shown that sensitization in patients with contact dermatitis was attributed to formaldehyde in occupations such as office worker, dialysis technician, machinist, garment workers, and printer and chemical worker.

The statistical data showed that between 1975 and 1993, the annual incidence of occupational contact allergy related to formaldehyde in textiles and clothing industries of Finland was 0.66/10, 000.

In Spain, cases of occupational allergic contact dermatitis due to formaldehyde and melamine/formaldehyde resin have also been reported, but most of them were outside the textile industry (De Groot et al. 2010b).

Cross-References

- ▶ Allergic Contact Dermatitis
- ▶ Contact Dermatitis in Children
- ▶ Nickel Allergic Contact Dermatitis
- ▶ Nickel Contact Dermatitis

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Titanium Alloy, Dermatitis, Allergic Contact, Granulomatous

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Synonyms

Contact dermatitis; Titanium

Delayed-type hypersensitivity reactions (type IV by Coombs and Gell) to metals like nickel or cobalt are quite common. In contrast, titanium is regarded as very stable material with almost no potency to elicit allergic contact dermatitis, thus often recommended as a substitute for patients suffering from nickel contact allergy and in need of a metal implant. However, it is discussed if titanium can elicit granulomatous reactions, which have been proposed as type V allergic reactions according to the classification of types I–IV hypersensitivity reactions by Coombs and Gell. These immune reactions are elicited by macrophages reacting to foreign body particles and usually appear several weeks after the uptake of the

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allergen, for example, as nodules mimicking hypertrophic scars or keloids after skin piercing.

Cross-References

- ▶ Allergic Contact Dermatitis
- ▶ Contact Dermatitis Due to Topical Drugs
- ▶ Nickel Allergic Contact Dermatitis

Topical Antihistamines

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Synonyms

Topical antihistaminic agents; Topical histamine antagonists; Topical histamine blockers

Definition

Topical antihistamines are applied to skin to provide relief of pruritus. Although antihistamines demonstrate H_1 and H_2 histamine receptor blockades, the exact mechanism of how they exert antipruritic effects remains unknown (Zonalon® and Benadryl® topical cream prescribing information). Two common uses for topical antihistamines are for temporary relief of pain and itching associated with multiple insults, including insect bites, minor skin irritations, and urushiol-induced contact dermatitis associated with the *Toxicodendron* genus in North America. There is an overarching question to the safety and efficacy of topical antihistamines.

Mechanism of Action

Histamine is an endogenous autacoid amine that has many important physiologic functions in neurotransmission, inflammation, and gastric acid secretion (Thurman 2008). Most notably, histamine is vital in mediating hypersensitivity and allergic responses. Histamine is stored in mast cells and basophils and can be released by antibodies, various pharmacological agents (e.g., vancomycin and morphine), and polypeptides (e.g., substance P). The release of histamine downstream binds to histamine receptors found both in the periphery (in smooth muscle cells and endothelial cells) and in the central nervous system (CNS). By binding to H_1 receptors on endothelial cells and smooth muscle cells, histamine mediates bronchoconstriction and vasodilation. Local vasodilation causes skin redness and vascular permeability, leading to the classic "wheal and flare" response (Thurman 2008). H_1 antagonists, such as diphenhydramine, are inverse agonists of the H_1 receptor and thus attenuate a primary step in the allergic response (Leurs et al. 2002). H_1 blockers comprise a large class of medications used in the treatment of allergy disorders and are commercially available in certain topical preparations. See Table 1 for drug information about topical antihistamines and Table 2 for dosing information.

Topical Antihistamines, Table 1 Drug information for topical antihistamines

Active ingredient	Common brand name	Strength	Dosage form
Diphenhydramine	Benadryl	2 %	Cream, gel, lotion
Doxepin	Prudoxin, Zonalon(R)	5 %	Cream

Pharmacokinetics

Topical doxepin demonstrates systemic absorption with serum concentrations up to 47 ng/mL. Evidence is limited for drug metabolism and biotransformation in human skin. Systemically, doxepin is metabolized by CYP P450 2D6 to an active metabolite, desmethyldoxepin. Both Doxepin and desmethyldoxepin undergo

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Topical Antihistamines, Table 2 Children and adult dosage information for topical antihistamines

Active ingredient	Adults and children >12 years	Children 6–12 years	Children 2–6 years
Diphenhydramine	Apply sparingly to affected area not more than three to four times daily	Apply sparingly to affected area not more than three to four times daily	Apply sparingly to affected area not more than three to four times daily
Doxepin	Apply a thin film four times each day with at least 3–4 h intervals between applications. Do not use beyond 8 days	NA	NA

further glucuronidation and are eliminated via the kidney (Zonalon® [prescribing information] 2007; Drake et al. 1999).

Topical diphenhydramine is absorbed, producing serum concentrations lower than assay detection. The extent of diphenhydramine metabolism in the skin is unknown. Systemically, diphenhydramine is metabolized to nordiphenhydramine, dinordiphenhydramine, and diphenylmethoxyacetic acid. From oral diphenhydramine studies, urine excretion of parent diphenhydramine is approximately 1 % (McEvoy 2006).

Clinical Trials

The most commonly prescribed topical antihistamines are diphenhydramine and doxepin (others have been studied, but are not available in the United States) (Eschler and Klein 2010). Although topical antihistamines are frequently recommended and prescribed by providers, there is a paucity of evidence for their efficacy in treating dermatologic allergic conditions.

Topical diphenhydramine has been available for nearly two decades; however, to date, there is a dearth of literature to support its use for topical application and antipruritic effects. An observational study evaluated the antipruritic effect in 22 patients with varying pruritic dermatoses receiving 2 % diphenhydramine ointment two to four times daily (Perry 1947). Moderate relief of itching was obtained in six patients, and excellent relief was obtained in two patients. Fifty percent of patients receiving placebo had similar antipruritic effects. The investigators concluded this formulation of diphenhydramine likely was not adequately absorbed to produce an antipruritic effect.

Doxepin is a tricyclic antidepressant that exhibits substantial antihistamine properties. A study involving 270 patients with moderate to severe pruritus for a minimum of 1 week secondary to atopic dermatitis were enrolled in a double-blind, vehicle-controlled, multicenter study (Drake et al. 1994). Patients were randomly assigned to 5 % doxepin cream ($n = 132$) or vehicle cream ($n = 138$), which was applied twice during the baseline visit and four times daily for the rest of the 7-day trial. Relief of pruritus was achieved in 85 % of doxepin-treated patients versus 57 % of vehicle-treated patients by day 7. Approximately 60 % of the patients in the doxepin group responded within the first 24 h compared to 41 % of patients in the vehicle group ($p < 0.01$). Visual analogue scales for pruritus severity and pruritus relief showed a significant improvement in the doxepin-treated group ($p < 0.01$). Nineteen patients withdrew from the study because of adverse effects (doxepin, $n = 16$; vehicle, $n = 3$). The most frequently reported adverse effects were localized stinging or burning (doxepin, $n = 39$; vehicle, $n = 34$) and drowsiness (doxepin, $n = 37$; vehicle, $n = 3$), all of which decreased in frequency and severity over time.

A study involving 11 patients with atopic eczema underwent a randomized, double-blind, placebo-controlled study for 3 days (Groene 2001). Patients' left and right arms were randomized according to treatment. Within each arm treated areas were randomized according

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to acetylcholine and sodium chloride. Patients were instructed to apply the creams (doxepin in either neutral cream base or neutral cream base alone) to the designated areas (25 cm^2) at the volar surface of the left or right forearm. On day four, patients returned to the clinic to receive acetylcholine, a pruritogenic mediator, or sodium chloride injections into the pretreated arms. Vasoreactions and cutaneous sensations were measured via laser Doppler fluxmetry. Doxepin treatment over 3 days reduced acetylcholine-provoked flare size more than 53 % ($p < 0.005$) and wheal size about 48 % ($p < 0.005$). However, antipruritic effect was similar to the neutral cream base. The itch intensity, which was expressed as the mean AUC value, was rated at 6.12 (0.3–15) arbitrary units after the neutral cream base application and 5.9 (2.9–11.2) arbitrary units after doxepin, respectively. Data from this study did not support the use of doxepin as an antipruritic. The neutral cream base likely demonstrated antipruritic action because of its rehydrating and moisturizing effects.

Safety and Adverse Effects

Topical doxepin is indicated for short-term use only (up to 8 days) due to the potential CNS side effects, such as drowsiness, which occurred in over 20 % of patients (Zonalon® [prescribing information] 2007). Caution is advised in those patients operating heavy machinery and the elderly population. Alcohol and initiating other sedating medications should be avoided while the patient is using topical doxepin. Patients also experienced having dry mouth and stinging and burning at the site of application, more often the placebo in clinical trials (Drake et al. 1994; Drake and Millikan 1995). Severe allergic contact dermatitis was reported in six patients after using doxepin 5 % cream for 2 weeks up to 7 months (Shelley et al. 1996). Some of these patients in the case report exhibited angioedema-like swelling, photodermatitis, and generalized weeping dermatitis were some of the reactions described. All patients were patch tested to rule out reaction to the cream's excipients. The authors suggested that doxepin's histamine blocking activity might augment cell-mediated hypersensitivity.

Topical diphenhydramine should not be used to cover large areas of the body. Death has been reported in case reports involving children less than 2 years of age (Turner 2009; Baker et al. 2003). Other adverse effects associated with topical diphenhydramine include skin irritation, photosensitivity, and rash.

Drug Interactions

Studies examining drug interactions have not been conducted in topical doxepin. Since plasma levels of topical doxepin can reach those exhibited by oral doxepin, drug interactions should be considered. Doxepin is metabolized by CYP P450 2D6; drugs that inhibit this enzyme (e.g., quinidine, cimetidine, and class I antiarrhythmic agents) can increase the concentration of doxepin. Additionally, monoamine oxidase inhibitors should be discontinued for at least 2 weeks before initiating topical doxepin (Zonalon® [prescribing information] 2007; Drake 2009).

There are no studies to date to indicate drug interactions with topical diphenhydramine.

Conclusion

Pruritus is frequently experienced in conditions such as eczema, insect bites, minor burns, sunburn, minor skin irritations, minor cuts, scrapes, and rashes due to poison ivy, poison oak, and poison sumac. Topical antihistamines are often prescribed or recommended, yet the efficacy of topical antihistamines is not well supported, as comprehensive reviews of their efficacy have been conducted (Klein and Clark 1999; Eschler and Klein 2010). Furthermore, these topical preparations may exacerbate patients' underlying condition.

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Cross-References

- Ocular Antihistamines
- Oral Antihistamines

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Topical Corticosteroids

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Synonyms

Topical glucocorticosteroids; Topical steroids

Definition

Topical glucocorticoids are commonly used in the treatment of rashes caused by allergic reactions, eczema, dermatitis, and other corticosteroid-responsive dermatoses. Topical corticosteroids have anti-inflammatory, antipruritic, and vasoconstrictive properties. All preparations have similar mechanisms of action but differ in the nature of their base and potency, thus allowing for a range of applications depending on the anatomic location and severity of the disease to be treated.

Mechanism of Action

The mechanism of action of glucocorticoids involves reducing the cellular inflammatory response. Mechanistically, the glucocorticoid (GC) binds to the glucocorticoid receptor (GR) complex (with several heat shock proteins, and other proteins), located within the cytoplasm of the target cell (Adcock 2001). The bound GC-GR complex is then translocated to the nucleus and in the nucleus, and interacts with GC responsive elements, subsequently altering gene transcription of certain key mediators in the inflammatory process (e.g., interleukins, chemokines, and phospholipase A_2) (Barnes et al. 1998).

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Through these expressive changes, macrophage and neutrophil migration to the area of inflammation is decreased (Uva et al. 2012).

Drug Information

Please refer to Table 1, Dosing of Commonly Prescribed Topical Corticosteroids, for a summary of generic and brand names, strengths available, and dosing.

Pharmacokinetics

Absorption/Distribution

Few, but older, studies exist that examine the pharmacokinetics of topical corticosteroids. Topical corticosteroids are absorbed through the stratum corneum over 6 h and can last for 16–24 h (Franz 1983). It was demonstrated that approximately 1 % of topical hydrocortisone was absorbed when placed on the forearm (Maibach 1976). The extent of percutaneous absorption of the topical corticosteroids is dependent on multiple factors, including epidermal integrity, pharmaceutical vehicle, application location, surface area, and temperature (Goa 1988). Additionally, the age of the patient plays an important role; younger children and the elderly population demonstrate increased drug absorption due to a thinner stratum corneum. Areas of the skin that have been compromised by abrasion/damage or inflammation generally have increased absorption after topical application. Areas that are occluded, such as the axilla or external genitalia, and areas where the stratum corneum is thin, including the eyelids, genitalia, and face, are shown to have a greater extent of absorption of topical glucocorticoids. Similarly, the use of occlusive dressings will enhance penetration into the skin, and could increase the possibility of systemic absorption (Pariser 1991).

Metabolism/Elimination

Evidence is limited for drug metabolism and biotransformation in human skin; however, evidence exists for betamethasone 17-valerate. Upon penetration of the stratum corneum, betamethasone is isomerized to 21-valerate and then cleaved by esterases in skin (Ademola and Maibach 1995). If the drug reaches systemic absorption, it is metabolized via same pathways as systemically administered corticosteroids, through hepatic transformation, and renal excretion.

Pharmacodynamics

Fluorinated corticosteroids (6 and/or 9 positions) have better penetration of the skin, which allows for treating affected areas with a thicker stratum corneum, such as the palmar and plantar regions. However, fluorination of the corticosteroid is not always directly related to potency (See Fig. 1). Fluorinated corticosteroids include amcinonide, clobetasol, clocortolone, desoximetasone, diflorasone, fluocinolone, fluocinonide, flurandrenonide, halcinonide, and halobetasol. Unlike nonfluorinated corticosteroids, application should be avoided, if possible, on areas of thinner stratum corneum. This reduces the potential of toxicities inherent in fluorinated compounds and potential dermal thinning (Goa 1988). Long-term use of potent topical corticosteroid use can lead to systemic side effects, including hypothalamic-pituitary-adrenal (HPA) axis suppression. HPA axis suppression can lead to decreased secretion of ACTH by the pituitary gland and decreased secretion of CRH by the hypothalamus. Left unchecked, suppression may lead to Cushingoid symptoms. Under rare instances, chronic HPA suppression may lead to acute adrenal crisis. Symptoms include fever, severe hypotension, shock, coma, and/or death (Hengge et al. 2006).

Selection of Topical Corticosteroids

The vehicle selected for delivery of the corticosteroid is also an important factor to consider when determining treatment of a patient. Ointments, occlusive tapes, and use of occlusive

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Topical Corticosteroids, Table 1 Dosing of commonly prescribed topical corticosteroids

Generic name	Brand name	Strength dosage form	Dosage instructions	Notes
Alclometasone	Aclovate	0.05 % Cream	**Adults, Adolescents, and Children >/= 1 year**: Apply a thin film to the affected area 2–3 times/day	
		0.05 % Ointment		
Amcinonide	Cyclocort	0.01 % Cream	**Adults, Adolescents, and Children**: Apply sparingly to the affected area 2–3 times/day	Fluorinated corticosteroid
		0.01 % Ointment		
		0.01 % Lotion		
Betamethasone Dipropionate	Betanate	0.05 % Cream	*Topical Dosage (Cream, lotion, and ointment)*:	
	Del-Beta	0.05 % Lotion		
	Diprolene	0.05 % Ointment	**Adults, Adolescents, and Children**: Apply a thin film to affected area 2–4 times/day	
	Diprolene AF	**Augmented Forms**: 0.05 % Cream/Gel/ Lotion/Ointment	Augmented gel, cream, ointment, or lotion is applied once or twice daily. Augmented products **not recommended** in children < = 12 years	
	Diprosone			
	Maxivate			
Betamethasone Valerate	Beta Derm	0.1 % Cream	*Topical Dosage (Foam)*:	
	Beta-Val	0.1 % Lotion		
	Betatrex	0.1 % Ointment	**Adults**: Apply 2 times/day to the scalp, morning and night	
	Valisone	0.12 % Foam		
	Luxiq			
Clobetasol Propionate	Clobevate	0.05 % Gel	*Topical dosage (non-emollient cream ONLY)*:	Fluorinated corticosteroid
	Clobex	0.05 % Shampoo		
	Cormax	0.05 % Lotion	**Adults, Adolescents, and Children >= 12 years**: Apply a thin layer to the affected skin areas twice daily	
	Olux	0.05 % Solution	*Topical dosage (emollient cream ONLY)*:	Limit treatment to 2 consecutive weeks and a maximum dose of 50 g per week
	Olux-E	0.05 % Ointment		
	Temovate	0.05 % Cream	**Adults and Adolescents >= 16 years**: Apply a thin layer to the affected skin areas twice daily	
	Temovate E	0.05 % Foam (Hydro-alcoholic)	*Topical dosage (topical/scalp solution)*:	Long-term use can lead to systemic side effects
		0.05 % Foam (Non-Aqueous)	**Adults, Adolescents, and Children >= 12 years**: Apply to the affected scalp areas twice daily	
		0.05 % Cream (Emulsified Base)	*Topical dosage (gel, foam, and ointment)*:	
			Adults, Adolescents, and Children >= 12 years: Apply to the affected areas twice daily	
			Topical dosage (lotion ONLY):	
			Adults: Apply to the affected areas twice daily. Rub in gently and completely	
Clocortolone	Cloderm	0.1 % Cream	**Adults and Adolescents**: Apply sparingly to the affected skin area(s) up to 3 times/ day. Rub in gently	Fluorinated corticosteroid
			Children: Apply sparingly to the affected skin area(s) up to 3 times/day. Rub in gently	Long-term use can lead to systemic absorption

(*continued*)

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Topical Corticosteroids, Table 1 (continued)

Generic name	Brand name	Strength dosage form	Dosage instructions	Notes
Desonide	Desonate	0.05 % Gel	*Topical dosage (topical cream, ointment, or lotion)*:	Treatment should be limited to 4 consecutive weeks
	Desonil	0.05 % Cream		
	DesOwen	0.05 % Lotion	**Adults**: Apply sparingly to affected areas. Cream or ointment may be used 2–4 times/day; lotion may be used 2–3 times/day	
	LoKara	0.05 % Ointment		
	Verdeso	0.05 % Foam	*Topical dosage (Foam or Gel)*:	
			Adults, Adolescents, Children, and Infants >= 3 months: Apply sparingly to affected areas twice daily	
Desoximetasone	Topicort	0.25 % Cream	**Adults, Adolescents, and Children >= 10 years**: Apply sparingly to the affected areas twice daily. Rub in gently	Fluorinated corticosteroid
	Topicort LP	0.05 % Cream		
		0.05 % Gel		
		0.25 % Ointment		
Diflorasone	Apexicon	0.05 % Ointment	*Topical dosage (non-emollient cream or ointment, high potency)*:	Fluorinated corticosteroid
			Adults and Adolescents: Apply a thin layer to the affected skin area(s) 1–4 times/day, depending upon the severity of the condition	
			Children: Apply a thin layer to the affected skin area(s) 1–2 times/day. Once daily treatment has been effective in pediatric populations	
	Apexicon E	0.05 % Cream	*Topical dosage (emollient cream or ointment, very high potency)*:	Long-term use can lead to systemic side effects
			Adults: Apply a thin layer to the affected skin area(s) 1–3 times/day, depending upon the severity of the condition	
			Children: In general, very high potency corticosteroids are not recommended in children. However, some studies have used superpotent corticosteroids once daily or twice daily	
Fluocinolone	Capex	0.01 % Shampoo	**Adults and Children**: Apply sparingly to the affected area 2–4 times/day, depending on the severity of the condition	Fluorinated corticosteroid
	Derma-Smoothe/FS	0.01 % Oil (Body/Scalp)		
	Synalar	0.025 % Cream		
		0.01 % Cream		
		0.025 % Ointment		
		0.01 % Solution		
Fluocinonide	Lidex	0.05 % Cream	**Adults, Adolescents, and Children >= 2 years**: Apply sparingly, 1–4 times/day to affected areas	Fluorinated corticosteroid
	Lidex-E	0.1 % Cream		
	Vanos	0.05 % Gel		
		0.05 % Ointment		
		0.05 % Solution		
		0.05 % Cream (Emulsified Base)		

(*continued*)

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Topical Corticosteroids, Table 1 (continued)

Generic name	Brand name	Strength dosage form	Dosage instructions	Notes
Flurandrenolide	Cordran	0.05 % Lotion	*Topical dosage (lotion, cream, or ointment)*:	Fluorinated corticosteroid
	Cordran SP	0.05 % Ointment		
	Cordran Tape	0.025 % Ointment	**Adults and Children**: Apply lotion, cream, or ointment sparingly, 2–3 times/day to affected areas	
		0.025 % Cream	*Topical dosage (tape)*:	
		0.05 % Cream		
		Impregnated Dressing	**Adults and Children**: The tape formulation is generally applied to a clean area every 12–24 h	
Fluticasone	Cutivate	0.05 % Cream	*Topical dosage (cream or ointment)*:	
			Adults and Adolescents: Apply sparingly to the affected area 2 times/day. Each treatment course may continue for up to 4 weeks	
		0.05 % Lotion	**Children and Infants >= 3 months of age**: Fluticasone cream 0.05 % applied sparingly to the affected area 1–2 times/day. In clinical trials, the 0.05 % cream has been applied once daily to children for the treatment of atopic dermatitis for up to 4 weeks	
		0.05 % Ointment	*Topical dosage (lotion)*:	
			Adults, Adolescents, and Children: Apply 0.05 % lotion sparingly to the affected area once daily. Each treatment course may continue for up to 4 weeks	
Halcinonide	Halog	0.1 % Cream	**Adults and Children**: Apply sparingly to the affected area 2–3 times/day, depending on the severity of the condition. Apply sparingly to affected area two to three times per day	Fluorinated corticosteroid
	Halog-E	0.1 % Ointment		
		0.1 % Solution		
Halobetasol	Ultravate	0.05 % Cream	**Adults**: Apply a thin layer to the affected skin areas 1–2 times/day, depending on the severity of the condition	Fluorinated corticosteroid
		0.05 % Ointment	**Adolescents and Children**: Apply a thin layer of cream to the affected area once daily in the morning, and apply a thin layer of ointment to the area once daily in the evening for 14 days. Do not use occlusive dressing	
Hydrocortisone	Ala-Cort	0.1 % Cream	*Topical dosage (0.5 % or 1 % OTC creams, ointments, sprays, or gels containing hydrocortisone or hydrocortisone acetate)*:	If condition worsens, or if symptoms persist for more than 7 days or clear up and occur again within a few days, therapy should be discontinued
	Caldecort	0.2 % Cream		
	Cortaid	0.5 % Cream		
	CortAlo	1 % Cream		
	Instacort 10	1 % Gel	**Adults, Adolescents, and Children >= 2 years**: For self-medication, apply to affected areas not more than 3–4 times/day	

(*continued*)

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Topical Corticosteroids, Table 1 (continued)

Generic name	Brand name	Strength dosage form	Dosage instructions	Notes
	Locoid	2 % Gel	*Topical dosage (hydrocortisone valerate or hydrocortisone)*:	
	Pandel	0.1 % Solution		
	NuCort	2.5 % Solution		
	NuZon	1 % Lotion	**Adults, Adolescents, and Children > 2 years old**: Apply sparingly to affected areas 2–4 times/day	
	Texacort	2 % Lotion	*Topical dosage (hydrocortisone acetate)*:	
	Westcort	2.5 % Lotion		
		0.2 % Ointment	**Adults, Adolescents, and Children > 2 years old**: Apply sparingly to affected areas 3–4 times/day	
		0.5 % Ointment		
		1 % Ointment	*Topical dosage (hydrocortisone butyrate)*:	
		2.5 % Ointment	**Adults**: Apply a thin film to the affected areas 1–2 times/day	
Mometasone	Elocon	0.1 % Cream	*Topical dosage (cream or ointment)*:	Resistant to metabolism in the skin, therefore, repeated application may lead to increased side effects and an increased risk of systemic absorption
			Adults: Apply a thin film to the affected areas once daily	
		0.1 % Lotion	**Adolescents and Children >= 2 years**: Apply a thin film to the affected areas once daily. Safety and efficacy of treatment for more than 3 weeks has not been established	
		0.1 % Ointment	*Topical dosage (lotion)*:	
			Adults: Apply a few drops to the affected areas once daily	
Prednicarbate	Dermatop	0.1 % Cream	*Topical dosage (cream)*:	
			Adults and Adolescents: Apply sparingly to the affected area 2 times/day	
		0.1 % Emollient Cream	**Children**: Apply sparingly to the affected area 2 times/day. Safe and effective use of the cream for > 3 weeks has not been established	
		0.1 % Ointment	*Topical dosage (ointment)*:	
			Adults, Adolescents, and Children >= 10 years: Apply sparingly to the affected area two times per day	
Triamcinolone	Kenalog	0.025 % Lotion	**Adults**: Apply 0.025–0.05 % cream, ointment, or lotion to the affected areas 2–4 times/day; 0.1–0.5 % cream, ointment, or lotion to the affected areas 2–3 times/day; or 0.015 % topical aerosol 3–4 times/day	Resistant to metabolism in the skin, therefore repeated application may lead to increased side effects and an increased risk of systemic absorption
	Pediaderm TA	0.1 % Lotion		
		0.025 % Ointment		
	Trianex	0.1 % Ointment		
	Triderm	0.05 % Ointment (Augmented)		
		0.05 % Cream		
		0.015 % Aerosol		

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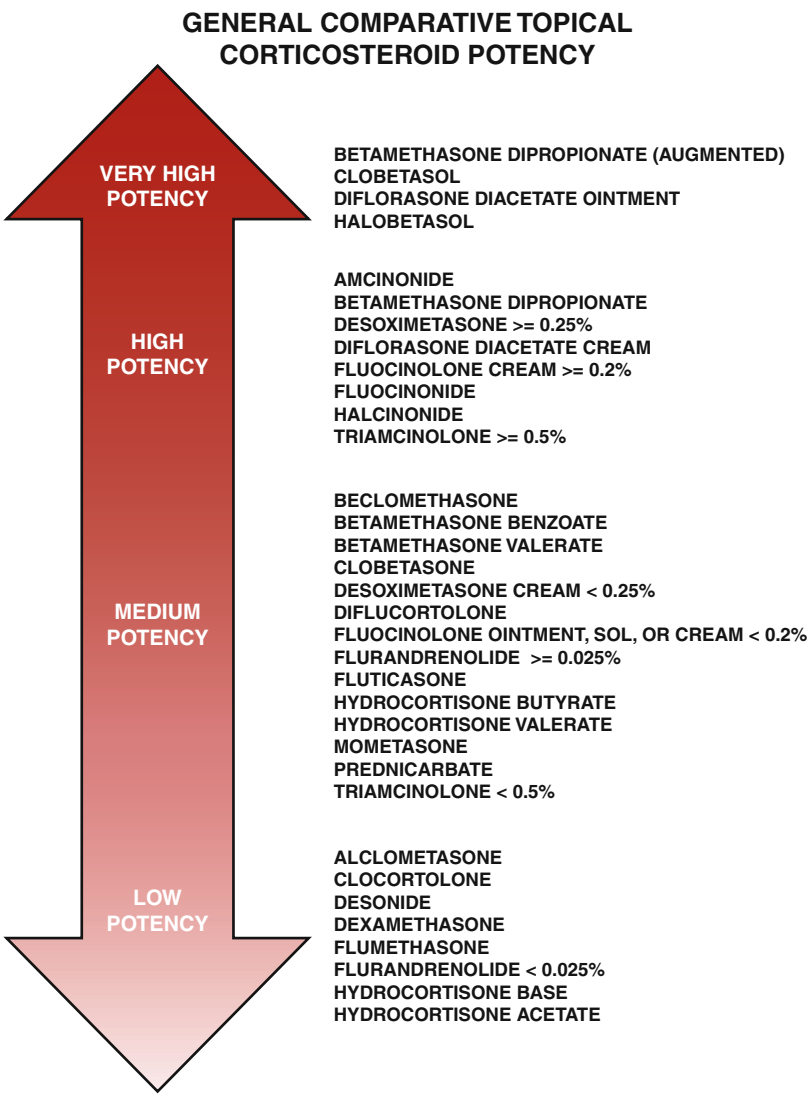

Topical Corticosteroids, Fig. 1 General comparative topical corticosteroid potency. Topical corticosteroids can be classified by their potency, ranging from low to very high. Potency is a crucial consideration for selecting an appropriate agent in order to maximize clinical outcomes and minimize the potential for adverse effects

dressings, all enhance penetration of the corticosteroid and have a hydrating effect on the skin. This can be beneficial for dermatoses associated with dry skin (Drake et al. 1996). Cream formulations are comprised of water suspended in oil, giving this base less occlusive properties than ointments and weaker penetration of the stratum corneum. In addition, creams often contain preservatives that can cause irritation and discomfort to the application site (Geraci et al. 1991).

Lotions and gels are much less lipophilic than ointments and therefore do not penetrate the skin as effectively. Additionally, being primarily water-based, these preparations can be easily washed away. Gels typically have a drying effect on the skin and should be used to treat areas such as the scalp and those that are occluded by other parts of the body. Both lotions and gels are also useful for application to hairy areas, because they penetrate easily while leaving very little residue behind. Foams, shampoos, and washes can be effectively applied to the scalp and other hairy areas, because they are easily spread and do not cause matting of the hair (Geraci et al. 1991).

Figure 1 illustrates general comparative potency of topical corticosteroids. Essentially,

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lower potency topical corticosteroids are utilized for areas of thinner skin and sensitive areas, especially areas under occlusion and intertriginous areas (Geraci et al. 1991). Low-potency topical corticosteroids have modest anti-inflammatory properties and are usually effective in treating acute inflammatory conditions. Low-potency topical corticosteroids are also considered the safest for continual use and are favored in the elderly or pediatric patients because of the decreased likelihood of adverse effects (Pariser 1991).

Topical corticosteroids with moderate potency are used for atopic dermatitis, nummular eczema, xerotic eczema, lichen sclerosis of the vulva, scabies and severe dermatitis (Tan et al. 2002; Renaud-Vilmer et al. 2004; Handa et al. 2001). Moderate topical corticosteroids are used in wider nonoccluded parts of the body such as the trunk, arms, and legs. Medium-to-high potency topical corticosteroids are also useful for treatment of areas with thickened stratum corneum (Geraci et al. 1991).

High potency topical corticosteroids are commonly used for psoriasis, lichen planus, chapped feet, severe poison ivy exposure, discoid lupus, alopecia areata, nummular eczema, and severe atopic dermatitis in adults. These topical corticosteroids are applied to limited skin areas to minimize systemic side effects. They are mainly indicated for use on areas of thickened stratum corneum.

Drug Interactions

There are no significant drug interactions associated with topical corticosteroids (Woo and Wynne 2011).

Conclusion

Millions of people are afflicted with skin diseases every year. Topical corticosteroids have become a mainstay treatment for these dermatologic conditions. The therapeutic effectiveness of corticosteroids is based primarily on their anti-inflammatory activity. Over the past five decades, topical corticosteroids have been used extensively resulting in improved treatment of dermatologic conditions with very few reported adverse events. Current studies are aimed at developing compounds that are locally potent and designed to have less potential to cause harmful effects. Prescribers' knowledge of factors such as potency, indications, corticosteroid vehicles, and frequency and duration of treatment is imperative to maximize clinical outcomes and minimize the potential for adverse effects. Special considerations should also be given to the pediatric and geriatric populations when selecting an appropriate agent.

Cross-References

- ▶ Allergic Contact Dermatitis
- ▶ Atopic Dermatitis
- ▶ Contact Allergy to Hair Dyes
- ▶ Cutaneous Drug Reactions
- ▶ Emergent Allergies in Cosmetics

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Topical Preparations: Calcineurin Inhibitors

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Synonyms

Anti-inflammatory agent; Immunosuppressant agent; Topical skin product

Definition

Topical calcineurin inhibitors (TCIs) are immunomodulatory preparations designed to suppress local immune-related reactions. Due to this mechanism of action, TCIs are approved for use in atopic dermatitis (AD) as second-line therapy (Astellas Pharma US, Inc 2012; Novartis Pharma Produktions GmbH 2011; Schneider et al. 2013). TCIs are often utilized in patients who have altered sensitivity to or poor therapeutic response with corticosteroid related treatment. In comparison to corticosteroids, TCIs can be used on most skin surface areas of the body as application does not result in skin atrophy and thinning (Schneider et al. 2013; Frankel and Qureshi 2012). Studies support the safety and efficacy of TCIs for treatment of AD; however, TCIs have not been studied in patients receiving treatment for greater than 1 year. Therefore, caution is warranted for long-term treatment of AD with TCIs.

Mechanism of Action

The mechanism of action of TCIs in atopic dermatitis is not known (Astellas Pharma US, Inc 2012; Novartis Pharma Produktions GmbH 2011). Systemically, calcineurin inhibitors bind to FK506 Binding Protein/macrophilin (FKBP-12) and inhibit calcineurin (a calcium-dependent phosphatase). This in turn inhibits T-cell activation by inhibiting gene transcription for cytokines such as interleukin-2 (IL-2), interferon gamma, and interleukin-4. Theoretically, through inflamed skin, TCIs are absorbed and inhibit activation of T-cells, dendritic cells, mast cells, and karatinocytes involved in the disease process of AD (Schneider et al. 2013; Frankel and Qureshi 2012).

Drug Information (Astellas Pharma US, Inc 2012; Novartis Pharma Produktions GmbH 2011)

Please refer to Table 1, Topical Calcineurin Inhibitors, for condensed drug information regarding generic and brand names, indication(s), dosing, contraindication(s), available products, etc.

Boxed Warning

The following warning is associated with both TCI products (Astellas Pharma US, Inc 2012; Novartis Pharma Produktions GmbH 2011).

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Topical Preparations: Calcineurin Inhibitors, Table 1 Drug information for topical calcineurin inhibitors

Topical calcineurin inhibitors		
Generic Name	Tacrolimus	Pimecrolimus
Brand name	Protopic®	Elidel®
Regulatory status	Prescription only	Prescription only
Indication	Second-line therapy for the short-term and non-continuous chronic treatment of **moderate to severe** atopic dermatitis in adults and children 2 years of age and older who are not immunocompromised and have either not responded to other topical treatments or when use of those other treatments is not advisable	Second-line therapy for the short-term and non-continuous chronic treatment of **mild to moderate** atopic dermatitis in adults and children 2 years of age and older who are not immunocompromised and have either not responded to other topical treatments or when use of those other treatments is not advisable
Contraindications	Hypersensitivity to tacrolimus or components of ointment	Hypersensitivity to pimecrolimus or components of cream
Available products	Ointment	Cream
	0.03 %; 30 g, 60 g, 100 g	1 %; 30 g, 60 g, 100 g
	0.1 %; 30 g, 60 g, 100 g	
Dosage and administration	Twice daily application of a thin layer of tacrolimus ointment to the affected skin only. Stop use when signs and symptoms resolve	Twice daily application of a thin layer of tacrolimus ointment to the affected skin only. Stop use when signs and symptoms resolve
Pregnancy category	C	C
Lactation warning	Tacrolimus is known to be excreted in human milk	It is unknown whether pimecrolimus is excreted in human milk
Special Populations	No dosing adjustment needs to be made for renal or hepatic impairment, or in geriatric patients	No dosing adjustment needs to be made for renal or hepatic impairment, or in geriatric patients
	Only the 0.03 % concentration is indicated for children 2–15 years old	Not indicated for use in children less than 2 years of age
	Not indicated for use in children less than 2 years of age	

Long-term Safety of Topical Calcineurin Inhibitors Has Not Been Established

Although a causal relationship has not been established, rare cases of malignancy (e.g., skin and lymphoma) have been reported in patients treated with topical calcineurin inhibitors.

Of note, the American Academy of Allergy, Asthma and Immunology (AAAAI), American College of Allergy Asthma and Immunology (ACAAI), Canadian Dermatology Association (CDA), and the Canadian Society of Allergy and Clinical Immunology (CSACI), have released position statements that promote the safety of TCIs. The position statements propose the warning is theoretical in nature as epidemiologic studies have found no association between TCI use and the occurrence of malignancy (Frankel and Qureshi 2012; Segal et al. 2013). While the warning was established based on case reports of malignancies and lymphoma in individuals utilizing TCIs, coupled with the mechanism of action for these medications, at this point, no evidence concluding this relationship has been documented or determined through case-control or long-term safety studies (Segal et al. 2013).

The following recommendations serve as safety precautions due to the potential risk of malignancy. Continuous long-term use of TCI's in any age group, is discouraged, and topical application should be limited to areas specific to treatment as patients with a larger BSA and those with abnormal epidermis may have increased percutaneous absorption leading to potential systemic absorption. Neither tacrolimus nor pimecrolimus are indicated for use in children less than two years old. TCI's should not be

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used in patients that are immunocompromised (Astellas Pharma US, Inc 2012; Novartis Pharma Produktions GmbH 2011; Schneider et al. 2013).

Adverse Reactions

Adverse reactions include localized reactions such as burning sensation and cutaneous infections (Chen et al. 2010). Reduction in application site reactions may be seen 3 days after initiation of therapy (Schneider et al. 2013). Neither phototoxicity nor photoallergenicity have been reported with TCI use (Astellas Pharma US, Inc 2012; Novartis Pharma Produktions GmbH 2011).

After 1 year of therapy, in comparison to corticosteroids, patients treated with TCIs report increased application site reactions, an equivalent risk of infection, and no significant risk of skin atrophy (Frankel and Qureshi 2012).

Drug Interactions

Drug interactions have not been systemically investigated with topical TCIs. Topical administration results in low blood levels of TCIs and, therefore, drug interactions are not expected (Astellas Pharma US, Inc 2012; Novartis Pharma Produktions GmbH 2011). TCIs are metabolized by CYP3A4 and should be used with caution with agents that are inhibitors of CYP3A4, such as erythromycin, itraconazole, ketoconazole, fluconazole, and cimetidine, as coadministration can result in increased TCI serum concentrations (Astellas Pharma US, Inc 2012; Novartis Pharma Produktions GmbH 2011).

Clinical Application and Comparative Efficacy

Pimecrolimus is approved for treatment of mild to moderate AD and tacrolimus is approved for treatment of moderate to severe AD. Several published sub-analyses have reported tacrolimus to be more efficacious and have a faster onset of effect than pimercrolimus in the adult population. Most of these studies evaluate the use of these two products over the course of 6 weeks; therefore, recommendations for comparative efficacy is lacking for longer durations of therapy (Meurer et al. 2002; Abramovits et al. 2008; Fleischer et al. 2007).

Numerous trials have investigated the effectiveness of TCIs versus corticosteroids in the treatment of AD. A meta-analysis of 25 clinical trials performed by Ashcroft et al. (2005) found that tacrolimus 0.1 % is as effective as potent topical corticosteroids (e.g., hydrocortisone butyrate 0.1 %) and more effective than mild topical corticosteroids (e.g., hydrocortisone acetate 1 %) for treating atopic dermatitis. The significance of this includes the ability to change therapy from potent topical corticosteroids to topical tacrolimus in order to prevent skin thinning and the ability to apply to sensitive areas such as the face. Although studies support the safety and efficacy of TCIs for treatment of AD, no data exists regarding treatment for greater than 1 year. Therefore, caution is warranted for long-term treatment of AD with TCIs.

Pimecrolimus was found to be less effective than betamethasone valerate 0.1 %, a potent topical corticosteroid (Ashcroft et al. 2005). Comparison to lower potency topical corticosteroids has not been performed. Because of these findings, pimecrolimus is indicated for mild to moderate atopic dermatitis as it was more effective than placebo in these patients.

Another meta-analysis by Chen et al. focused on 20 clinical trials performed in pediatric patients (Chen et al. 2010). Both tacrolimus ointment and pimecrolimus cream were found to be safe and effective for atopic dermatitis. The comparative results suggest that tacrolimus 0.03 % and tacrolimus 0.1 % had comparable effectiveness and tacrolimus ointment was more effective than pimecrolimus cream in the pediatric population (Chen et al. 2010).

Cross-References

▶ Allergic Contact Dermatitis
▶ Atopic Dermatitis

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Tracheobronchomalacia and Hyperdynamic Airway Collapse

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Synonyms

Bronchomalacia; Excessive dynamic airway collapse; Hyperdynamic airway collapse; Tracheobronchomalacia; Tracheomalacia

Definition

Tracheobronchomalacia and hyperdynamic airway collapse refer to the loss of the structural integrity of the airway walls. It may or may not result in symptoms of dyspnea on exertion, a nonproductive cough, or wheezing.

Introduction

Tracheobronchomalacia (TBM) and hyperdynamic airway collapse (HDAC) can be debilitating diseases associated with decreased functional capacities and a poor quality of life. The diverse etiologies associated with TBM and HDAC can obscure and delay an accurate diagnosis for years (Carden et al. 2005). A thorough medical history is important to understanding the possible etiologies as well as guiding the diagnostic testing. The medical history may also suggest what treatments may be most beneficial. This review will exclude the discussion of pediatric TBM as it is fundamentally different and is largely comprised of congenital diseases that rarely affect adults. Given that there is no standard definition of this complex disease and there are numerous terms used to describe the disease, searching the literature can be challenging (Murgu and Colt 2006).

Description

TBM and HDAC present in a similar fashion although they are fundamentally different entities. Confounding the issue is the fact that they can coexist. In individuals with structurally normal airways, the cross-sectional area of the airway can narrow up to 35 % with forced expiratory maneuvers such as coughing or exercise (Murgu and Colt 2006; Boiselle et al. 2009). When the cross-sectional area of the airway decreases more than 50 %, it is considered abnormal (Carden et al. 2005; Murgu and Colt 2006). TBM refers to the loss of structural integrity of the cartilaginous structures within the airway (Murgu and Colt 2006). Airway walls become

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"soft" and lead to increased airway mobility and flattening of the normally curved cartilaginous structures with pressure changes that occur with coughing or forced expiratory maneuvers (Carden et al. 2005; Murgu and Colt 2006). HDAC is an exaggeration of the normal airway wall movement (Murgu and Colt 2006). In HDAC airway compromise is due to excessive mobility of the posterior membrane into the airway lumen (Murgu and Colt 2006). In some cases, patients may have elements of incompetent cartilaginous structures (TBM) as well as excessive movement of the posterior membrane (HDAC) (Carden et al. 2005; Murgu and Colt 2006).

Prevalence

The prevalence of TBM and HDAC is not known. In study populations, the incidence varies dependent on the definition and test used to diagnose TBM or HDAC. The incidence of TBM or HDAC ranges between 4 % and 23 % in patients undergoing bronchoscopy for evaluation of respiratory complaints (Carden et al. 2005; Murgu and Colt 2006; Ochs et al. 2009; Jokinen et al. 1977). Ten percent of patients being evaluated for suspected pulmonary embolism by chest computed tomographic scanning fit the criteria for TBM in one retrospective series (Hasegawa et al. 2003).

Pathophysiology

The specific pathologic process is dependent on the etiology of TBM of HDAC. In-depth insight into the histopathology of TBM is limited although a few case series provides some information (Murgu and Colt 2006). The cartilaginous rings are the main sites of pathologic abnormality in TBM. The ratio of cartilage to soft tissue is decreased (Murgu and Colt 2006). The decrease in cartilaginous tissue results in abnormal structural integrity. The loss of structural integrity is the principal mechanism in TBM.

In HDAC the posterior membrane of the airway is redundant or lacks the ability to maintain normal tone (Murgu and Colt 2006). With normal inhalation, the posterior membrane of the airway moves posterior and increases the luminal area of the airway. Longitudinal smooth muscle fibers tighten to prevent overdistention. With exhalation the posterior membrane moves forward into the lumen of the airway. Longitudinal smooth muscle fibers again tighten to prevent excessive airway compromise. Studies providing histopathology demonstrate decreased smooth muscle fibers in patients with HDAC allowing for exaggerated airway movements (Murgu and Colt 2006).

Patients with TBM and HDAC have shortness of breath with activity, cough, and wheezing (Murgu and Colt 2006). They also have an inability to effectively clear secretions, which predisposes to recurrent infections (Murgu and Colt 2006). The ineffective mucociliary clearance as well as the predisposition to develop recurrent infections may create significant airway inflammation and perpetuate further damage to the airway.

Etiology

TBM and HDAC that develop in adults are acquired and often attributable to a known entity (Table 1). Several etiologies that cause TBM and HDAC are a result of inflammation within the airway wall. Prolonged intubation or the prolonged presence of a tracheostomy tube may result in structural weakening of the airway wall at the site of balloon inflation (Norwood et al. 2000). Chronic inhalation or aspiration of substances that result in irritation of the airway can weaken the airway wall. Examples of inhaled substances include tobacco smoke or fumes from the combustion of fossil fuels (Murgu and Colt 2006). Materials aspirated into the airway include aspiration of gastric acid or food particles. Inflammation of airway soft tissue and cartilaginous structures can result from collagen vascular diseases including relapsing polychondritis (Carden et al. 2005; Murgu and Colt 2006; Ernst et al. 2009). Chronic infections of the airway can be associated with airway

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Tracheobronchomalacia and Hyperdynamic Airway Collapse, Table 1 Etiology of TBM and HDAC. Many different etiologies can be associated with TBM and HDAC. Airway inflammation and injury to the airway are the most common causes of adult-acquired TBM and HDAC. A thorough history and physical as well as a careful review of the patients' diagnostic information may suggest the etiology (Carden et al. 2005; Ernst et al. 2009; Jokinen et al. 1977; Murgu and Colt 2006; Norwood et al. 2000)

Inflammation
Chronic airway infections
Inhalation of airway irritants (Tobacco smoke, combustion of fossil fuels)
Aspiration of gastric acid and food particles (GERD)
Collagen vascular diseases (e.g. Relapsing Polychondritis)
COPD
Asthma
Balloon trauma from prolonged endotracheal intubation or Tracheostomy
Injury to the Airway
Chest trauma
Lung cancer
Non-malignant chest anomalies (intra-thoracic thyroid goiter, aortic or pulmonary vessel aneurysm, bronchogenic cysts)
Tracheal surgery (lobar resection, lung transplant)
Tracheal or bronchial electrocautery or laser therapy
Congenital diseases presenting in adulthood
Mounier-Kuhn Syndrome (congenital tracheobronchomegaly)
Ehlers-Danlos syndrome

Tracheobronchomalacia and Hyperdynamic Airway Collapse, Table 2 Signs, and symptoms of TBM and HDAC. Signs and symptoms attributable to TBM and HDAC are nonspecific. Patients failing to improve with aggressive treatment of their suspected respiratory diagnosis should be evaluated for TBM and HDAC (Carden et al. 2005; Murgu and Colt 2006)

Shortness of breath with exertion
Cough ("barking seal")
Recurrent chest infections
Difficulty clearing secretions
Wheezing
Hemoptysis
Syncope related to coughing

inflammation and can lead to diminished integrity of the airway wall (Carden et al. 2005; Murgu and Colt 2006; Jokinen et al. 1977). Chronic obstructive pulmonary disease and asthma have been associated with TBM and HDAC. The relationship with these common clinical entities is believed to be due to chronic airway wall inflammation as well as pressure changes in the chest promoting large airway collapse (Carden et al. 2005; Murgu and Colt 2006).

Injury or manipulation of the airway can be associated with TBM (Carden et al. 2005; Murgu and Colt 2006). Chest trauma can result in fracture of tracheal cartilages that can result in structurally weakened airway walls. Lung malignancies can destroy the airway wall or mechanically compress the airway. Nonmalignant chest lesions (thoracic thyroid goiter, aortic or pulmonary vessel aneurysm) can also compress the airway leading to TBM. Patients who have had airway surgeries, endobronchial electrosurgery, or laser therapy can develop focal TBM or HDAC.

Rare congenital diseases associated with TBM and HDAC can present in adulthood. Mounier-Kuhn syndrome (also known as congenital tracheobronchomegaly) is characterized by atrophy or absence of elastic fibers of the posterior membrane leading to large airways with minimal integrity (Carden et al. 2005). Ehlers-Danlos syndrome is an inherited collagen vascular disease associated with weakened and lax cartilaginous structures leading to TBM (Murgu and Colt 2006).

Signs and Symptoms

Signs and symptoms of TBM and HDAC are nonspecific (Table 2). Consideration and further testing should be sought in patients who fail to respond to usual and customary treatments for their suspected diagnosis. Patients with TBM and HDAC may have an intractable cough, wheezing, shortness of breath with exertion, and recurrent infections (Carden et al. 2005; Murgu and Colt 2006). Shortness of breath and a cough that worsen with exercise are the principle complaints of patients with TBM and HDAC. Inhalation is not difficult for patients with TBM and

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Tracheobronchomalacia and Hyperdynamic Airway Collapse, Table 3 Diagnostic testing for TBM and HDAC. Pulmonary function testing should be obtained in all patients being evaluated for TBM or HDAC. Recognition and aggressive treatment of patients with respiratory diseases that coexist with TBM and HDAC may improve their respiratory symptoms. CT of the chest with dynamic expiratory imaging is a valuable test. Chest CT may provide a specific etiology which can explain the patients' complaints and offer therapeutic guidance. Bronchoscopy with airway exam is the gold standard for diagnosing TBM and HDAC. Bronchoscopy allows for identifying the location of TBM or HDAC, grades the severity of collapse, and provides an opportunity to biopsy the affected tissue or collect airway cultures. Nasogastric pH or impedance probe testing can confirm the diagnosis of reflux in patients who are suspected of having reflux-associated TBM or HDAC (Carden et al. 2005; Murgu and Colt 2006; Kovesi and Rubin 2004)

Test	Findings: TBM and HDAC	Rational
Pulmonary function testing	Decreased expiratory flow with abnormal flow volume loop Notching or sawtooth-type deflections may be seen in the expiratory flow loop	Determine severity of pulmonary limitations; identify coexistent asthma or COPD
Computed tomography of the chest with dynamic expiratory imaging	Diminished size of airway lumen with forced expiration	Grade severity of airway narrowing. Suggest etiology responsible for TBM or HDAC and guide management
Bronchoscopy with expiratory maneuvers	Airway caliber narrowing with expiratory expiration	Grade severity of airway narrowing. Possible biopsy of airway wall. Collect airway cultures
pH or impedance probe testing	Acid and nonacid reflux to the proximal esophagus and the oropharynx	Treating reflux may reduce symptoms related to TBM and HDAC. Diminished acid exposure may stabilize the airway

HDAC, whereas exhalation can be difficult with some patients feeling that they cannot fully exhale.

Diagnosis

TBM and HDAC are difficult to diagnose. The diagnosis is often delayed due to the nonspecific symptoms and the overlap with many other respiratory illnesses (Carden et al. 2005). Once TBM and HDAC are suspected, the diagnostic approach should be uniformed and directed based on the history and results from prior testing (Table 3). Initial studies should include pulmonary function testing and computed tomography (CT) of the chest with dynamic expiratory imaging (Carden et al. 2005; Murgu and Colt 2006). Pulmonary function testing delineates the physiological limitation of the airway and excludes severe asthma or chronic obstructive pulmonary disease (COPD) (Murgu and Colt 2006). Asthma and COPD can coexist with or be the cause of TBM and HDAC. Careful clinical reason should be exercised in the setting of mild TBM or HDAC with severe symptoms of asthma or COPD. Although TBM and HDAC can contribute to a patients' shortness of breath, it is not likely the sole etiology, and the severe asthma or COPD should be treated aggressively.

Chest CT scanning with dynamic expiratory imaging is a valuable test. The chest CT will identify the severity of TBM and HDAC as well as identify the anatomy of the chest to effectively identify any contributing lesions (Carden et al. 2005; Murgu and Colt 2006). The CT scan will identify whether TBM or HDAC is the primary clinical entity or suggest that it is the result of another diagnosis. The CT scan may identify a specific clinical entity, which may suggest a specific clinical treatment.

Bronchoscopy is a valuable tool in the diagnostic evaluation of TBM and HDAC. Bronchoscopy allows for an evaluation of the tracheal and bronchial tree with tidal respirations and with forced expiration. Bronchoscopy is considered the gold standard to diagnose TBM and HDAC (Carden et al. 2005). It is not the intent of the bronchoscopy to elicit coughing. The bronchoscopist should also be careful not to overly sedate the patient. Coughing can elicit violent movements of the airway and may result in airway

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collapse in individuals with mild TBM or HDAC and in some patients with normal airways. Sedation should be minimal and allow the patient to follow commands. The intent of the bronchoscopy is to visualize the airway with full inspiration and forceful exhalation. The bronchoscopy allows for an assessment of the severity of airway narrowing as well as the location of the airway narrowing. In selected patients, bronchoscopy also allows for endobronchial biopsies to assist in the diagnosis.

Patients with complaints of gastroesophageal reflux or who have findings of an abnormal esophagus on chest imaging should have a pH or impedance probe test. A pH or impedance probe test will identify the presence of acid and nonacid reflux. Cessation of aspirated acid and nonacid gastric material can decrease airway inflammation. Decreasing airway inflammation may reverse the injury to the airway wall (Kovesi and Rubin 2004). If nonsurgical means to reduce aspiration fail, consideration should be given to a surgical procedure (such as Nissen fundoplication in case of significant hiatal hernia) to reduce or eliminate acid and nonacid reflux (Kovesi and Rubin 2004).

Classification

It is important to identify the location, type, and severity of TBM and HDAC. Therapeutic decisions may be dependent on the location, type, and severity. Distal airway involvement in TBM and HDAC is not amenable to airway stenting or surgical intervention. Medical management is the only option for patients who have distal TBM and HDAC. Tracheal and/or proximal main stem bronchi may be amenable to airway stenting and surgical interventions.

The nature or description of airway luminal narrowing may provide clues to the causative etiology. Saber-sheath trachea is primarily associated with chronic obstructive pulmonary disease (Murgu and Colt 2006). Circumferential airway narrowing and severe airway flattening can be seen with relapsing polychondritis and in situations with severe airway inflammation which decrease the structural integrity of the cartilaginous structures of the airway (Ernst et al. 2009) (Fig. 1).

The severity of TBM and HDAC dictates the intensity of the treatment that patients receive. Patients with mild (luminal narrowing of 50–70 %) and moderate (luminal narrowing of 70–90 %) TBM and HDAC are treated with medical management with a focus on the primary etiology. Patients with severe luminal narrowing (greater than 90 %) and severe symptoms receive aggressive treatment. Patients with severe TBM and HDAC receive targeted treatments to their primary inciting etiology as well as consideration for stent placement and surgical airway intervention (Carden et al. 2005; Murgu and Colt 2006).

Treatment

Treatment of TBM and HDAC is dictated by symptoms and severity. Treatment is not warranted in patients with severe TBM or HDAC and no clinical symptoms. An alternate etiology should be sought for patients with severe respiratory symptoms and only mild TBM or HDAC. Aggressive therapy should be pursued in patients with moderate to severe TBM or HDAC and clinical symptoms consistent with TBM or HDAC.

Medical therapy should be included in the treatment plan for every patient with TBM and HDAC (Carden et al. 2005; Murgu and Colt 2006). Medical treatment may be sufficient dependent on the clinical situation and the suspected (or diagnosed) clinical etiology of TBM or HDAC (Carden et al. 2005; Murgu and Colt 2006). Appropriate management of severe reflux or aspiration and severe recurrent infections may sufficiently resolve symptoms of TBM and HDAC in some patients (Carden et al. 2005; Murgu and Colt 2006; Ernst et al. 2009).

Weight management should be included in the treatment regimen for TBM or HDAC. As the abdomen and chest wall become more obese, the configuration of the chest cavity changes with elevation of the diaphragm. The changes in the diaphragm serve to foreshorten the trachea and can decrease the rigidity of the trachea.

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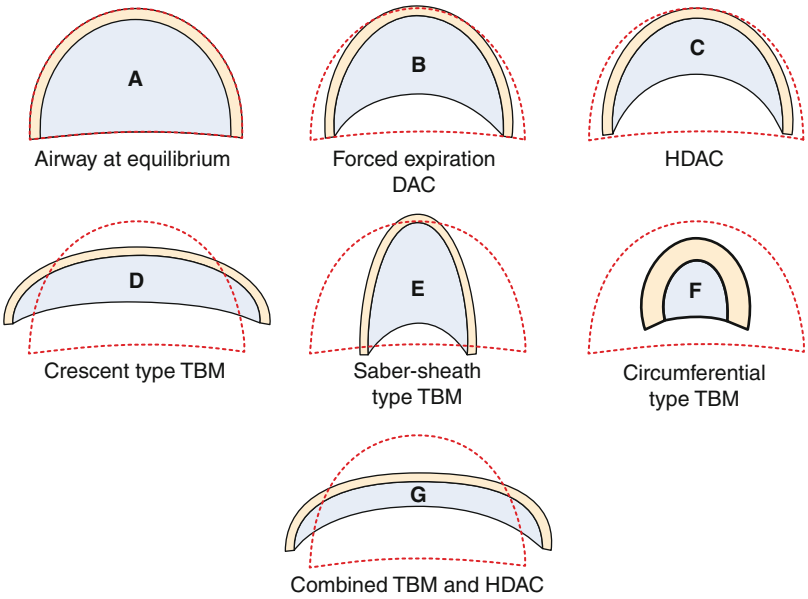

Tracheobronchomalacia and Hyperdynamic Airway Collapse, Fig. 1 The above figure depicts different types of TBM and HDAC. Item *A* represents a normal trachea at equilibrium; note that the posterior membrane is flat. In items *B* through *G*, the *red dotted line* represents the trachea at equilibrium with the colored item representing change due to forced expiration. Item *B* represents forced exhalation in the normal individual with the posterior membrane bulging forward into the lumen of the airway. Item *C* represents forced exhalation in hyperdynamic airway collapse with the posterior membrane bulging into the lumen of the airway and occluding more than 50 % of the airway lumen. In item *C* the integrity of the tracheal ring is intact, and the abnormality is associated with the posterior membrane. Item *D* represents crescent-type TBM manifesting with flattening of the tracheal rings and loss of structural integrity of the cartilaginous structures. In item *D* the membranous portion of the trachea is flat and does not bulge into the lumen of the airway; the site of pathology is the tracheal cartilage. Item *E* represents saber-sheath-type TBM and manifests with inward movement of the lateral walls. Item *E* is seen in patients with advanced COPD. Item *F* represents concentric TBM with anterior and lateral wall movement. Item *F* is seen with severe airway inflammation. Item *G* represents combined TBM and HDAC. In item *G* the cartilaginous structures flatten and the posterior membrane bulges into the airway lumen (Figure reproduced with approval from the Pakistan Journal of Chest Medicine – Seaman and Musani 2012)

The decrease in structural integrity of the trachea allows for a decrease in the amount of pressure required to collapse or narrow the trachea. Weight loss can result in a normal position of the diaphragm and serve as an effective treatment.

Aggressive and maximal treatment of COPD and asthma should be rendered to patients with coexistent TBM and HDAC (Carden et al. 2005; Murgu and Colt 2006). If maximal treatment of COPD or asthma results in resolution of respiratory complaints, then no further airway interventions should be explored. Exercise programs such as pulmonary rehabilitation should be encouraged to educate patients about proper breathing techniques.

A therapeutic trial of noninvasive positive pressure ventilation (NIPPV) trial should be considered in patients who have coexistent obstructive sleep apnea and severe TBM or HDAC. NIPPV can effectively treat OSA associated with TBM or HDAC as well as improve mucociliary clearance (Murgu and Colt 2006). NIPPV serves to pneumatically stent the airway. Pneumatic airway stenting may decrease airway inflammation by enhancing airway clearance and thus treating TBM and HDAC (Murgu and Colt 2006; Adliff et al. 1997).

Patients with collagen vascular-associated diseases (such as relapsing chondritis) may be effectively treated with immune suppression (Ernst et al. 2009). Aggressive immune suppression

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may increase airway wall integrity by decreasing cartilage inflammation thereby stabilizing the airway wall.

Definitive surgical treatment should be considered for patients who are aggressively treated with medical management and continue to have symptoms due to TBM or HDAC. Patients with TBM or HDAC should have a stent trial to document improvement in their symptomatology and an objective improvement in their functional status (Majid et al. 2008). A stent trial involves the placement of an inverted "Y" silicone stent into the patient's airway. The silicone stent is inserted using a rigid bronchoscopy. The stent is positioned in the trachea and extends into the left and right main stem bronchi. The stent is usually left in place for 10–14 days. Improvement in a patients' functional capacity (objectively measured by a 6-min walk test), in the ability to perform day-to-day activities, or in pulmonary physiology (as measured by pulmonary function testing) is suggestive of improvement after definite surgical intervention. Long-term use of airway stents should be avoided due to the incidence of complications including inspissation of secretions and granulation tissue (Ernst et al. 2007). Patients who do not improve with a therapeutic stent trial should not be considered for surgical intervention. Surgical intervention involves suturing the posterior membrane to a mesh-like material to increase the stiffness and rigidity of the posterior membrane (Majid et al. 2008). This surgical procedure requires a lengthy operation time. Only selected centers and surgeons specifically trained in this type of airway reconstructive surgery should be considered in this labor-intensive procedure. This involved surgical intervention improves respiratory symptoms, health-related quality of life, and functional status in patients who have a dramatic improvement with their stent trail (Majid et al. 2008).

Laser therapy has been used to treat HDAC (Murgu and Colt 2006). Patients with HDAC that involves focal areas of the membranous portion of the trachea or bronchi can be treated with topical laser therapy (Murgu and Colt 2006). The intent is to induce scarring that contracts the posterior membrane and stiffens the posterior membrane preventing collapse (Murgu and Colt 2006; Dutau and Breen 2010).

Future directions include the development of biogenic stents that slowly become integrated into the airway wall. Ideal biogenic stents could be placed in a minimally invasive fashion, allow for normal mucociliary clearance, and enhance airway wall integrity. This type of biogenic stent would be very desirable and may have increased utility.

Conclusion

TBM and HDAC can be difficult to diagnose and are indistinguishable at the time of presentation. TBM and HDAC differ in the airway anatomy affected. The prevalence of TBM and HDAC in the general population is not known but may be as high as 25 % in some populations. TBM and HDAC should be considered in patients with significant respiratory complaints without a defined respiratory diagnosis. Diagnostic testing for TBM and HDAC includes computed tomographic scan of the chest, pulmonary function testing, and a careful clinical evaluation with additional testing directed by clinical findings and preliminary test results. Management of patients with TBM and HDAC includes aggressive medical therapy as indicated. Patients who fail to improve with aggressive medical management should proceed to a stent trial. An airway stent trial is used to select patients who will benefit from airway reconstructive surgery. Patients who have symptomatic and functional improvement with a stent trial should proceed with airway reconstructive surgery. Airway stenting is not an optimal long-term treatment due to stent-related complications.

Cross-References

- ▶ Asthma Variants: Cough-Variant Asthma
- ▶ Diseases in DDx of Asthma: COPD
- ▶ Diseases in DDx of Asthma: Differential Diagnosis of Asthma
- ▶ Testing: High-Resolution Chest Computed Tomography Scan

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U

Urticaria

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Synonyms

Hives; Nettle rash; Urtication

Definition

Urticaria is characterized by itching hives and presents a group of diseases which share a characteristic skin reaction pattern. It can be subdivided in acute spontaneous urticaria with symptoms lasting for less than 6 weeks and chronic urticaria, in symptoms recurring over a longer period.

Clinical Manifestation

Urticaria is known as one of the most frequent conditions and is often seen in emergency care units. Lifetime incidence is higher than 20 %, about two third of spontaneous urticaria is acute and one third is chronic with almost daily symptoms, and it can persist for years. Because of the disturbing symptoms quality of life as well as occupational disability is significantly impaired. The itchy wheals are short-lived, elevated erythematous lesions which can occur anywhere on the body (Fig. 1).

In about half of the patients also relapsing, angioedema is reported and while systemic reactions due to the urticaria such as fatigue, respiratory, gastrointestinal, and arthralgic symptoms are rather rare; the occurrence of angioedema can become dangerous. It often involves the eyelids, lips, genitalia, and sometimes the tongue or laryngo-pharynx, which can become life threatening (Fig. 2). In contrast to hereditary C1-esterase-inhibitor-deficient angioedema, recurrent angioedema without urticaria is considered to be histamine mediated and can be observed in 10–20 % of the patients with normal C1-esterase-inhibitor.

Urticaria can be classified into three subtypes. About 80 % of urticaria is of spontaneous type, about 10 % provoked by physical stimuli (physical urticaria), and less than 10 % of special type. Physical urticaria is a distinct group caused by cold air/water/wind (cold urticaria), vertical pressure (delayed pressure urticaria, latency of 3–8 h), local heat (heat urticaria), UV and/or visible light (solar urticaria), mechanical shear forces (dermographic urticaria) or vibratory forces (vibratory urticarial/angioedema) and should be clearly distinguished from spontaneous urticaria. In special types the wheals do not occur spontaneously

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Urticaria, Fig. 1 Disseminated urticarial lesions on the leg

Urticaria, Fig. 2 Angioedema of the lips

or by physical triggers. An example is cholinergic urticaria which is caused by a short increase in body temperature, e.g., by physical exercise, passive warmth or emotional stress. This subtype is common in young adults and resolves spontaneously. Other examples of special subtypes are contact urticaria (triggered by contact urticariogenic substance) or aquagenic urticaria (triggered by water) (Zuberbier et al. 2009a; Wedi and Kapp 2005). Of note, two urticaria subtypes can coexist in the same patient (e.g., spontaneous urticaria and dermographic uricaria).

Pathogenesis

Wheals are caused by local vasodilatation and increase in capillary permeability with plasma leakage, either IgE mediated or due to non-immunologic activation of mast cells and basophils both of which results in mediator release, especially histamine. Mast cells are predominantly located near to blood vessels, adnex, and nerves. Possible mechanisms by which degranulation is induced include autoreactivity including autoimmunity mediated by functional autoantibodies directed against the high-affinity IgE receptor (FcεRI) or IgE, infections (e.g., with helicobacter pylori), non-allergic hypersensitivity reactions (e.g., to acetylsalicylic acid), as well as direct liberation of histamine due to, e.g., neurotransmitters (substance P) or complement activation, bacterial toxins, and other by now not detected pathways (Federman et al. 2003; Wedi et al. 2004). Angioedema is caused by similar mechanisms, but is localized deeper in the dermis, subcutaneous, and submucosal tissues.

The mechanism of autoreactivity was by now only confirmed in chronic spontaneous urticaria. In about 30 % of the patients, IgG and/or IgE antibodies against the high-affinity IgE receptor (FcεRI) or IgE and their functional activity (such as histamine release, cysteinyl leukotriene production) in basophil granulocytes and mast cells were detected. In another subpopulation, a positive autologous serum test provides evidence for autoreactivity, but there is no correlation to the findings of autoantibodies against IgE and FcεRI. Finally, the exact role and the

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way of activation remains unclear regarding autoreactivity as well as the other possible eliciting factors.

Diagnosis

If a cause in acute urticaria cannot be identified by history and physical examination (infection?), no further investigations are needed due to the self-limiting nature. In recurrent angioedema, hereditary (only 5 % of all angioedema without urticaria) and acquired (very rare) angioedema due to C1-inhibitor deficiencies must be excluded. Due to the heterogeneous etiology of chronic urticaria, the diagnostic schedule should include a careful search for persistent infections with helicobacter pylori, streptococci, staphylococci and perhaps yersinia, non-allergic triggers (e.g., nonsteroidal antirheumatics, particularly acetylsalicylic acid, rarely also food additives), and autoreactive mechanisms (autologous serum skin test, thyroid autoantibodies) (Zuberbier et al. 2009b; Wedi and Kapp 2005). In physical urticaria diagnosis is made by careful history and standardized physical tests (e.g., pressure tests with defined weight, cold exposure).

Management

Except for acute spontaneous urticaria, therapy can be problematic and is not standardized. Identified trigger factors should be eradicated (e.g., infections) or avoided (e.g., nonsteroidal antirheumatics, food additives, physical trigger factors; also unspecific stimuli like alcohol and overheating) (Zuberbier et al. 2009b; Wedi and Kapp 2007a). The mainstay is symptomatic treatment with low-sedating H1 antihistamines in sufficient dose, considering potential side effects and local treatment with antipruritic and cooling lotions. Glucocorticosteroids (20–40 mg prednisolone equivalent) should be reserved for exacerbations and only given as short course. Medical supervision (inpatient care) is recommended in case of dyspnea, hypotension, and generalized severe urticaria. In refractory cases, drugs not licensed for urticaria like leukotriene antagonists or cyclosporine have been successfully administered. Furthermore, omalizumab, an anti-IgE antibody, has shown promising results in clinical trials.

It is discussed that adequate treatment of acute spontaneous urticaria is able to inhibit the progression to chronic spontaneous urticaria. However, there is no prognostic factor identifying patients at risk for progression to chronic urticaria. Prognosis of physical urticaria is worse than other subtypes of chronic urticaria, particularly in dermographic urticaria and delayed pressure urticarial (Zuberbier et al. 2010; Wedi and Kapp 2007b).

Cross-References

- ▶ Contact Urticaria and Protein Contact Dermatitis (to Asparagus, Cow's Hair, Seafood, Etc.)
- ▶ Immunomodulator Therapy of Chronic Urticaria
- ▶ mAbs (omalizumab)
- ▶ Mast Cell Mediators
- ▶ Mast Cells
- ▶ Oral Antihistamines
- ▶ Role of Mast Cells in Diseases

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V

Venom Content

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Synonyms

Antigen 5; Hyaluronidase; Hymenoptera venom proteins; Insect venom allergens; Phospholipase; Protease

Definition

Venoms of social Hymenoptera consist of a variety of proteins, peptides, and other small molecules. Many of these molecules are bioactive. This entry concentrates on the venom constituents that are allergens, contributing to an IgE-mediated immune response.

Hymenoptera Venoms

Social Hymenoptera have venoms specialized for defense and occasionally other functions such as killing or paralyzing prey. Many of the constituents are bioactive peptides and other smaller organic molecules with widely different functions and properties. Many of the proteins and larger peptides can function as allergens in humans, inducing IgE antibody formation and causing allergic reactions upon subsequent stings. There are excellent reviews of the smaller molecules in honeybee venom (Banks and Shipolini 1986), vespid wasp venoms (Nakajima 1986), and ant venoms (Schmidt 1986). The venom protein allergens from many of the more important insects responsible for allergic reactions have been extensively studied and reviewed through early 2008 (King and Spangfort 2000; Hoffman 2006; Hoffman 2008a, b). A complete list of recognized venom allergens can be accessed at the official site of the WHO/IUIS Allergen Nomenclature Sub-Committee, www.allergen.org. Three-dimensional structures have been determined for a number of venom allergens listed in Table 1.

Venom allergens have both peptide-/protein- and carbohydrate-based allergenic determinants. IgE antibodies against the carbohydrate epitopes lead to a cross-reactivity of indeterminate clinical significance. Carbohydrate-free recombinant allergens have been used to identify the sensitizing insect species by in vitro testing.

Venomics

Several recent studies have utilized the techniques of modern proteomics to study insect venoms. The examination of the venom content of the Brazilian paper wasp, *Polybia paulista*

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Venom Content, Table 1 Three-dimensional structures of insect venom allergens

Allergen	Function/family	Protein database entry, www.rcsb.org
Honeybee		
Api m 1	Phospholipase A_2	1POC
Api m 2	Hyaluronidase	1FCU, 1FCQ, 1FCV, 2 G88
Api m 4	Melittin	2MLT
Yellowjacket		
Ves v 2	Hyaluronidase	2ATM
Ves v 5	Antigen 5	1QNX
Imported fire ant		
Sol i 2	Pheromone-binding protein	2YGU
Sol i 3	Antigen 5	2VZN

(dos Santos et al. 2010), is an excellent example. The authors were able to identify 84 different proteins belonging to three groups: venom proteins, muscle proteins, and housekeeping proteins probably from the venom gland. The major proteins are the expected well-characterized venom proteins: phospholipase A_1B, hyaluronidase, antigen 5, and venom serine protease. There are smaller amounts present of a number of additional serine proteases and metalloproteases, heat shock proteins, protease inhibitors, and vascular endothelial growth factor and small amounts of the enzymes phospholipase A_2, arginine kinase, and alpha-glucosidase and a homolog of fire ant protein Sol i 2. Particularly interesting is the finding of small amounts of the proteins usually associated with other groups of stinging insects. Phospholipase A_2 and CUB protease are associated with bees, Sol i 2 is associated with ants, and arginine kinase is a major toxin in endoparasitoid wasps.

Bee Venoms

Honeybees

The venom of the honeybee, *Apis mellifera*, is a common cause of allergic reactions to stings. The Africanized bee is a subspecies with identical proteins in the venom. There are a number of additional species of honeybee found in Asia, some of which are used commercially. There are ten characterized allergens in *A. mellifera* venom.

Api m 1 is phospholipase A_2, a glycoprotein of 16 kDa. It is the most important allergen in the venom and is about 16 % of the protein. The carbohydrate is attached to asparagine 16 and is a series of alpha 1,3 fucosylated glycoforms. IgE antibody binding is highly conformation dependent and the carbohydrate contributes to both the protein and carbohydrate epitopes. Api m 1 has been extensively studied as a model for venom immunotherapy including peptide and modified protein therapies. The phospholipases of the Asian species *A. cerana* and *A. dorsata* have amino acid sequences that are 96 % and 92 % identical to Api m 1.

Api m 2 is the enzyme hyaluronidase, which is a spreading factor dissolving intracellular ground substance. It is a glycoprotein of 39 kDa and an important allergen. It is closely related to mammalian hyaluronidases. IgE antibody binding is dependent on native conformation. The carbohydrate groups are similar to those of Api m 1. Similar enzymes are present in venoms of other bees and wasps. The enzyme from *Apis cerana* venom is 94 % identical.

Api m 3 is acid phosphatase, originally named allergen B. The enzyme is more similar to mammalian prostatic acid phosphatases than to lysosomal enzymes. It is a glycoprotein of 43 kDa, mainly present as a noncovalently associated homodimer.

Api m 4 is the amphipathic, membrane-active peptide melittin. The conformation is an alpha helix. The 3 kDa molecules are found mainly as noncovalent tetramers at high concentration. Melittin makes up about 50 % of the dry weight of honeybee venom. It is responsible for the pain of honeybee stings and can lyse cells at high concentrations. It is one of the most thoroughly studied peptides. A minority of honeybee allergic patients have IgE antibody to Api m4, and the fraction increases with subsequent stings and immunotherapy. Other honeybee species have melittins with minor differences in amino acid sequence.

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Api m 5, the 100 kDa protein originally named allergen C, has recently been found to be dipeptidylpeptidase IV (Blank et al. 2010). About half of honeybee venom allergic patients react to it. Dipeptidylpeptidase IV cleaves dipeptides ending in alanine or proline from the N-terminus of peptide chains. It converts promelittin to the membrane-active melittin as it travels down the venom duct from the venom gland to the venom sac.

Api m 6 is a series of splice variant peptides of about 8 kDa. About 40 % of honeybee venom allergic patients have IgE antibodies reacting with Api m 6.

Api m 7 is the 39 kDa CUB serine protease. This molecule has a CUB domain which functions in protein-protein interactions in the complement system and bone formation. The protease domain is a typical insect serine protease similar to prophenoloxidase-activating factor, although it has a bulky methionine residue at the entrance to the binding pocket. Bulky residues in this position are found in a number of other insect serine proteases. Its activity is unknown.

Api m 8 is a carboxylesterase of 70 kDa. It may have acetylcholinesterase activity.

Api m 9 is a serine carboxypeptidase of 60 kDa.

Api m 10 is an interesting glycoprotein allergen named icarapin or carbohydrate-rich protein. Its molecule weight varies from 50 to 55 kDa. There are numerous glycosylation sites. Recent studies (Blank et al. 2011) have shown that the nonglycosylated recombinant molecule has significant IgE antibody-binding activity.

Bumblebees

There are numerous members of the genus *Bombus*, but only two have been studied in relation to venom allergy. *B. pennsylvanicus* is a North American species that tends to nest in yards especially in wooden objects with openings like bird houses. *B. terrestris* is a European species that has been partially domesticated and is used to pollinate vegetable crops in hothouses. Bumblebee venoms are similar to honeybee venoms but contain smaller amounts of peptides named bombolitins and do not contain melittin. IgE antibodies from individuals sensitized by field stings may be cross-reactive with honeybee venom, but IgE from patients from individuals with occupational allergy is usually specific for bumblebee.

The group 1 allergens are phospholipase A_2, similar to honeybee. They contain fucosylated carbohydrate attached to asparagine 19. Both Bom t and p 1 are 54 % identical to Api m 1.

Bumblebee venom contains a group 4 allergen that is not present in significant quantity in honeybee venom. Bom 4 is a tryptic serine protease of 27 kDa. It is highly active enzymatically and easily hydrolyzes a variety of substrates including casein. The majority of sensitized patients have IgE antibody against the protease.

Vespid Venoms

Vespid wasps are members of the superfamily *Vespoidea*. They include yellowjackets of the genus *Vespula*, hornets of the genera *Dolichovespula* and *Vespa*, and paper wasps of the genera *Polistes* and *Polybia*. The venoms of these insects are all similar. IgE from sensitized individuals demonstrate varying degrees of cross-reactivity, with less between more distant groups. Rare subjects have antibodies that can distinguish between the two major species groups of yellowjackets. Cross-reactivity between yellowjacket and hornets is common, and there is less cross-reactivity between yellowjacket and paper wasp. Paper wasp venom-sensitized patients can usually distinguish venoms from North American species from venoms of European species. Vespid venoms do not contain melittin, but peptides called mastoparans, which are potent releasers of mediators including histamine from mast cells.

Yellowjackets and Hornets

The group 1 allergens of vespids are phospholipases totally different from honeybee phospholipase A_2. The proteins are about 34 kDa and have phospholipase A_1B activities. They are members of the lipoprotein lipase family, missing the lid

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region. Many species including the white-faced hornet have two different forms which are 67 % identical to each other.

Group 2 allergens are hyaluronidases similar to honeybee. There are usually two variants in each species. Vespid hyaluronidases are weakly allergenic with most of their IgE reactivity caused by cross-reactive carbohydrate or cross-reactions with honeybee.

The recently characterized group 3 allergens are dipeptidylpeptidase IV. It is similar to the honeybee enzyme and functions to activate toxic peptides.

The group 5 allergens are members of a large family of proteins called antigen 5/CAP. This family appears in most if not all eukaryotes. In plants it occurs as pathogenesis-related proteins, in helminths as excretory-secretory proteins produced at maturation, in snake venoms and in mammals as cysteine-rich secretory proteins and a human glioma tumor antigen. This group of allergens has been studied extensively and numerous sequences are available. Allergenic cross-reactivity parallels sequence similarity and phylogenetic difference. Some species express two or three antigen 5 genes of differing sequence.

Paper Wasps

Paper wasp venoms have an additional allergen, not found in significant amounts in yellowjacket or hornet venoms. The group 4 allergen is a 33 kDa single domain serine protease. It is enzymatically active, but its specificity is unknown. It contains carbohydrate and induces IgE antibody formation.

Ant Venoms

Ants are phylogenetically related to vespid wasps. Ant venoms are highly variable, with those of some species containing wasp like allergens, others peptides, organic molecules, and a large group of common ants have formic acid venoms. Only those venoms containing proteins and large peptides cause allergic reactions. Ant venom allergens have recently been reviewed (Hoffman 2010).

Fire Ants

Fire ants belong to the genus *Solenopsis*, which originated in the Americas. Several species have been carried around the temperate and subtropical world as tramps by commerce. The native species in the United States have been almost totally replaced by *S. Invicta* from South America. The largest component of fire ant venoms is water insoluble piperidine alkaloids (Brand et al. 1972). The alkaloids cause the wheal and flare reaction minutes after a sting and the sterile pustules that form the in about 12 h. Fire ant stings are extremely potent IgE antibody inducers, and the venom contains four characterized allergens.

Sol i 1 is a phospholipase A_1B of 38 kDa similar to the vespid enzyme. It contains N-linked carbohydrate. A fraction of yellowjacket venom-sensitized individuals produce IgE antibody which cross-reacts with Sol i 1. These individuals may experience allergic reactions to their first fire ant sting.

Sol i 2 is a disulfide-linked homodimer of 14 kDa chains. Recently the three-dimensional structure has been determined (Borer et al. 2012). Although the group 2 allergens are not related to other characterized protein families by sequence, the three-dimensional structure suggests that they are related to pheromone-binding proteins. The recombinant molecules have high affinities for hydrophobic pheromone-type molecules including isocaryophyllene, decane, and beta-farnesene. Group 2 allergens have a lower degree of sequence conservation than the other allergens. Sol i 2 and r 2 are 78 % identical and some species-specific IgE antibodies are observed. The group 2 allergens are the highest concentration proteins in the venoms.

Sol i 3 is a member of the antigen5/CAP family of 26 kDa. The three-dimensional structure has been determined (Padavattan et al. 2008). There is very little surface conservation between Sol i 3 and vespid wasp antigen 5′s, consistent with the observation that there is little or no IgE antibody cross-reactivity.

Sol i 4 is a monomer of 12 kDa and a member of the Sol i 2 family. It has one less cysteine residue than Sol i 2 monomers. There is little or

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no group 4 allergen in *S. richteri* venom, but it is present in *S. geminata* venom.

Bulldog and Jack Jumper Ants

The primitive Australian ants of the genus *Myrmecia* have highly allergenic venoms. The venom of *M. pilosula* has been extensively studied (Wiese et al. 2006). The characterized allergenic molecules are hetero- and homodimers of peptide chains of around 5–7 kDa called pilosulins. There are several uncharacterized proteins which also bind IgE antibodies from sensitized individuals. The strongest binding bands were at 26 and 90 kDa.

Needle and Samsum Ants

The ponerine genus, *Pachycondyla*, originally native to the Far East and the Middle East has been spread to numerous locations by commerce. Only one allergen in the venom has been characterized, a member of the Sol i 3/antigen 5 family with 54 % identity to Sol i 3 (Lee et al. 2009). Some sera from patients sensitized to samsum ants show a limited cross-reactivity with fire ant venom.

Harvester Ants

Stings from harvester ants of the genus *Pogonomyrmex* occasionally cause allergic reactions. The venom contains phospholipase A and B activity, hyaluronidase, phosphatase, esterases, and hemolytic peptides. No venom allergens have been characterized.

Cross-References

- ▶ Biting Insects (Systemic and Local Reactions)
- ▶ Honeybee Allergy
- ▶ IgE Testing
- ▶ Immunotherapy, Mechanisms
- ▶ Imported Fire Ant Allergy
- ▶ Insect Allergy in Children
- ▶ Specific IgE
- ▶ Vespid Allergy: Yellow Jackets, Hornets and Wasps

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Vespid Allergy: Yellow Jackets, Hornets and Wasps

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Synonyms

Hymenoptera venom allergy; Insect sting allergy; Sting anaphylaxis

The Insects

Allergic reactions can occur to insect stings or bites, but anaphylaxis occurs predominantly from stings and rarely from bites. Stinging insects are all of the order Hymenoptera which includes several important families. This entry will review the allergic reactions to the vespid genera of stinging insects including the genus Polistes, the genus Vespula, and the very closely related genus Dolichovespula. The family of vespids includes the insects that cause the majority of allergic reactions to stings. The common term "wasp" has been used in both lay and medical literature to include all of the vespid genera (yellow jackets, hornets, and Polistes wasps), but we will reserve the term wasp for insects of the genus Polistes. Although the other members of the vespid family (genus Vespula and Dolichovespula) are closely related and their venoms are highly cross-reactive, the Polistes wasps are only partially related to (and partially cross-reactive with) the other vespid genera (Hoffman 1981). The Polistes wasps are not as common as the yellow jackets as causes of allergic reactions in most geographic areas, but they can predominate in some warmer climates such as the Gulf states (Louisiana and Texas) and the Mediterranean countries of Europe (Italy and Greece).

The Polistes wasps include many species distributed through most parts of the world. They are mostly social insects that build nests which are generally smaller than other vespid nests and lacking the outer paper layers such that the open cells are visible. These nests can house less than a dozen to several dozen insects and are typically located around the frames of windows and doors, under wood railings, and inside hollow fence posts. Some wasp species are solitary (e.g., mud daubers) and are much less commonly implicated in allergic reactions to stings. Wasps can vary considerably in color, including black, red, and brown wasps, and the Mediterranean wasp (P. dominulus) has the same markings as yellow jackets. All Polistes species have the characteristic body that can distinguish them from yellow jackets, including the "wasp waist" and legs that dangle as they fly.

The Vespula are most commonly known as yellow jackets, of which there are many species throughout the world. They are social insects that build nests which can contain hundreds or thousands of insects. The nests are usually underground or tunneled into natural or man-made features of the landscape and are encased in an outer paper shell. The Dolichovespula, also described as aerial yellow jackets, usually build nests in trees or bushes. Dolichovespula arenaria is known as a yellow hornet, and D. maculata is known as a white-faced (or bald-faced) hornet, which is a distinctly larger insect than the other Vespula genera. The Dolichovespula are not considered true hornets. The hornets are members of another vespid genus, Vespa, which is very closely related to the Vespula. Vespa crabro is a European hornet that does have a presence in the USA. Vespa orientalis is an Asian hornet not found in the Americas. The vespid insects are attracted to food, and stings often occur when food or drink is present. They are also highly sensitive to vibration and will attack when their nest is disturbed. Some species release an attack pheromone when they sting which often results in multiple additional stings.

The Venoms

Allergic reactions to insect stings are directed against antigens in the venom that is injected

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into the skin during a sting. Wasp and vespid venoms also contain vasoactive amines and small molecules that are the cause of the burning, itching, pain, and local swelling that are normal features of a sting. The venom allergens are proteins most of which have known enzymatic activity, including a hyaluronidase and a phospholipase (Hoffman 1981). The major allergens of wasp and vespid venoms are antigen 5 (Pol v 5 and Ves v 5, respectively) which have no known activity and are common to all the species of the vespid genera: Polistes, Vespula, Dolichovespula, and Vespa. These allergens have been sequenced and recombinant allergen proteins have been prepared and studied. Wasp venom also contains proteases which are the major allergen in the Mediterranean wasp P. dominulus, rather than the phospholipase and antigen 5 as in North American wasps. These wasps have increased in number in the Northeastern United States and may cause allergy that could go undetected by tests using commercial wasp venoms. The venom protein allergens of all the vespid venoms are highly cross-reactive, but unique allergenic determinants are present in each venom such that genus-specific sensitivities exist in some patients.

Wasp venom has significant cross-reactivity with other vespid venoms, but RAST-inhibition studies show that about 50 % of wasp allergic patients have IgE antibodies to unique wasp allergens that do not cross-react with yellow jacket venom. The venom protein allergens of all the wasp species venoms are highly cross-reactive with each other, but unique allergenic determinants are present in each venom such that species-specific sensitivities exist in some patients. Although most patients are allergic to the common wasp and vespid species in any geographic area, there are individuals who have very specific allergy to individual or local species.

The Reactions

Insect stings normally cause pain, itching, and swelling in the area of the sting. The discomfort usually subsides gradually over a period of hours but can remain mild for a few days. Some people get larger than normal swellings due to nonspecific sensitivity of the skin. Allergic reactions can be local or systemic (Bilo and Bonifazi 2008; Golden et al. 1989). Large local reactions are generally minimal in the first few hours after the sting but become progressively more swollen for 24–48 h, reaching sizes of 10–20 cm or larger and subsiding slowly over 5–10 days. These reactions are IgE-dependent late-phase inflammatory responses to venom allergens. Although not usually dangerous, large local reactions can cause vascular or nerve compression resulting in "compartment syndrome" and could cause airway obstruction if the sting occurs in the pharynx or airway. Large local reactions are often mistaken for cellulitis especially when there are lymphangitic streaks. However, the reaction occurs after 1–2 days, whereas cellulitis would take 4–5 days or longer to develop.

Systemic reactions to stings include the entire spectrum of anaphylaxis (Lieberman 2010). The mildest systemic reactions are limited to cutaneous symptoms and signs (flushing itching, urticaria, angioedema), which in themselves do not meet the criteria for (multisystem) anaphylaxis, but can be generalized and frightening when severe. Moderate systemic reactions usually include the cutaneous manifestations as well as limited airway or vascular symptoms (dizziness, throat tightness, breathing discomfort). Severe reactions cause marked hypotension and/or dyspnea, and extreme (near-fatal) reactions cause unconsciousness and hypoxemia. Other elements of anaphylaxis can include abdominal and GI symptoms or a variety of cardiac manifestations (MI or arrhythmia). Insect sting anaphylaxis can be biphasic or protracted and may require repeated doses of epinephrine and prolonged supportive care with intravenous fluids and medications.

The Diagnosis

The diagnosis of insect sting allergy requires a clear history of reaction consistent with the patterns described above. Confirmatory tests are

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usually performed with venom skin tests because they have greater sensitivity than in vitro tests (Golden et al. 2011; Bilo et al. 2005). Skin tests using the intradermal technique are usually required to identify the presence of venom-specific IgE, but concentrations greater than 1 mcg/ml can cause nonspecific irritative reactions thus limiting the diagnostic range of the procedure and sometimes leading to false-negative results. Serologic tests for venom-specific IgE, most commonly the ImmunoCAP-FEIA, have less sensitivity than skin tests but can be positive in some skin test-negative patients. Improvements in the technology have permitted a lower threshold for detection and therefore improved sensitivity. In vitro methods using recombinant allergens may have greater specificity, but would have to contain the full range of component allergens to have adequate sensitivity and rarely equal the accuracy of skin tests. Basophil activation tests have been described that provide an alternative mechanism to identify allergic responsiveness to venoms. These tests have been reported to have improved predictive value for clinical outcomes but are complex and costly to perform, and their value may be limited to patients with negative skin tests and serum IgE tests. Unlike skin tests, the basophil activation tests can be interpreted in numerous ways that define positive and negative results and have not been compared to the gold standard test – sting challenge.

The prognosis is of critical importance in determining the need for preventative treatment. Predicting the risk of future allergic reactions to stings requires not only a complete clinical history and appropriate diagnostic tests but also an understanding of the natural history of insect sting allergy (Bilo and Bonifazi 2009; Golden et al. 1997). Early studies revealed that the reaction to a sting can be unpredictable. The presence and level of IgE (by skin or serum tests) predict the frequency but not the severity of reaction to a sting (Golden et al. 2006; Reisman et al. 1985). In patients with a clear history of systemic reaction to stings and positive venom IgE tests, a challenge sting will cause systemic reaction in only 30–70 % depending on the severity of previous reactions and other risk factors. It is not known why approximately 50 % of such patients do not react to a sting challenge, but repeat sting challenge will cause a reaction in 20 % of those who did not react to the first sting. This variability may be due to endogenous variability in the patient or to variable intensity of stings. The utility of sting challenge as a diagnostic procedure is limited because of the need for 2 stings at different times, the availability of insects of known species, and the logistics of performing the sting challenge, as well as ethical considerations (given the risk of a life-threatening reaction). The relative risk of anaphylaxis to a sting is related to numerous factors including the severity of previous sting reactions, the level of baseline serum tryptase, the type of insect (greater with honeybee), and abnormal levels of other mast cell mediators (e.g., PAF) (Rueff et al. 2009; Golden et al. 2006; Muller 2009). The chance of a severe sting reaction is lower in children than in adults. Patients who have had only large local reactions to stings have less than 5 % chance of anaphylaxis to a subsequent sting, as do children who have had only mild (cutaneous) systemic reactions to stings (Valentine et al. 1990; Golden et al. 2009). The risk in adults with cutaneous reactions is less clear, but prospective studies show minimal risk of progression to more severe reactions (Golden et al. 2006).

The Treatment

Treatment of acute insect sting anaphylaxis is the same as any other form of anaphylaxis, requiring epinephrine injection and often intravenous fluids and oxygen (Lieberman et al. 2010). There is no contraindication to the administration of epinephrine to a patient in anaphylaxis. There is no immediate benefit from antihistamines or corticosteroids. Close observation in an emergency department is recommended because of the risk of recurrent, biphasic, or protracted anaphylaxis. There is no evidence that steroids prevent biphasic anaphylaxis. Large local reactions can be treated symptomatically with cold compresses

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and oral antihistamines, but when severe may benefit from a few days or oral glucocorticoid medication.

Prevention of insect sting anaphylaxis can include avoidance and precautions (Clark and Camargo 2006). Carrying an epinephrine autoinjector can help to treat anaphylaxis when it occurs, but the only way to prevent reactions and restore a normal quality of life is with venom immunotherapy (VIT) (Oude-Elberink et al. 2002). Venom immunotherapy is indicated in patients who have had a systemic reaction to a sting and have evidence of venom-specific IgE antibodies on skin or serum tests (Golden et al. 2011; Bonifazi et al. 2005). Children with mild (cutaneous) systemic reactions do not require VIT because they have <3 % chance of anaphylaxis to a future sting (Golden et al. 2004; Valentine et al. 1990). Adults with cutaneous systemic reactions (urticaria/angioedema) may also have relatively low risk of anaphylaxis, but are generally advised to be treated with VIT because the risk of life-threatening anaphylaxis is greater in adults than in children (Lockey et al. 1988; Golden et al. 2004; Golden et al. 2011).

Controlled trials show that VIT is more than 90 % effective in completely preventing systemic allergic reactions to insect stings (Hunt et al. 1978). Using partially purified commercial venom extracts, VIT can give full protection within days or weeks of beginning treatment. The initial buildup of the dose can be accomplished in hours (ultra-rush), days (rush), weeks (modified rush), or months (traditional) using different regimens. The maintenance dose for each venom is 100 mcg. Once achieved, this dose is administered every 4 weeks for at least 1 year, and the interval may then be increased to 6–8 weeks over 2–3 years. Adverse effects include local swelling which are generally tolerated and systemic reactions ranging from a few hives to severe anaphylaxis. Severe reactions occur in 5 % of patients during the initial buildup but are very infrequent during maintenance treatment (Muller and Haeberli 2005). Treatment is recommended for 5 years in most cases, for 3 years in some patients at relatively lower risk (history of mild systemic reactions and many children), but 10 years or longer in high-risk patients (very severe sting reactions, elevated baseline serum tryptase, systemic reaction during treatment, frequent unavoidable exposure) (Golden et al. 1998, 2000, 2011; Lerch and Muller 1998; Muller 2009; Niedoszytko et al. 2009; Reisman and Lantner 1989; Reisman 1993; Rueff et al. 2009). The long-term outcome (15–30 years) in these high-risk patients has not been reported. VIT is not normally recommended for patients with large local reactions because of the low risk of anaphylaxis, but may be considered for patients with frequent and severe large local reactions because it has been proven effective to reduce morbidity and avoid the need for steroid treatment (Golden et al. 2009).

Conclusion

Insects of the vespid family include yellow jackets, some hornets, and wasps. Insects of the Polistes genus include many species of wasps. Allergic sensitization to venom proteins can lead to sting reactions that range from very large swellings to anaphylaxis. Insect sting allergy is diagnosed by detailed history and is confirmed using specific venom skin tests or in vitro methods to detect venom-specific IgE antibodies. Treatment recommendations are based on history, diagnostic tests, and a knowledge of the natural history of the disease and known high-risk factors such as elevated baseline serum tryptase. Venom immunotherapy is highly effective to prevent allergic reactions to stings and is as safe as any other type of specific allergen immunotherapy. VIT induces a tolerance that persists long after treatment is discontinued, usually after 5 years of VIT.

Cross-References

- ▶ Allergen Immunotherapy, Overview
- ▶ Biting Insects (Systemic and Local Reactions)
- ▶ Diagnostic Components: Allergen for In Vivo (Skin Testing, Immunotherapy) and In Vitro (Serology) IgE Antibody Testing

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- ▶ Honeybee Allergy
- ▶ IgE Testing
- ▶ Immunotherapy, Mechanisms
- ▶ Imported Fire Ant Allergy
- ▶ Insect Allergy in Children
- ▶ mAbs (Omalizumab)
- ▶ Mastocytosis
- ▶ Safety of Immunotherapy
- ▶ Venom Content

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